THE THERAPEUTIC AGENTS OF THE QUINOLINE GROUP

CINCHOPHEN, PLASMOQUINE, NUPERCAINE, QUININE AND ACRIDINE DYES

The Relation between their Chemical Constitution and Pharmacologic Action

BY

W. F. von OETTINGEN, M.D., Ph.D.

ASSISTANT PROFESSOR OF PHARMACOLOGY, SCHOOL OF MEDICINE,
WESTERN RESERVE UNIVERSITY, CLEVELAND, OHIO

A C S

American Chemical Society
Monograph Series

BOOK DEPARTMENT

The CHEMICAL CATALOG COMPANY, *Inc.*

330 WEST FORTY-SECOND STREET, NEW YORK, U. S. A.

1933

Printed in the United States of America by
J. J. LITTLE AND IVES COMPANY, NEW YORK

THESE PAGES ARE DEDICATED TO

TORALD SOLLMANN, M.D.,

THE MASTER AND ADVISOR.

GENERAL INTRODUCTION

American Chemical Society Series of Scientific and Technologic Monographs

By arrangement with the Interallied Conference of Pure and Applied Chemistry, which met in London and Brussels in July, 1919, the American Chemical Society was to undertake the production and publication of Scientific and Technologic Monographs on chemical subjects. At the same time it was agreed that the National Research Council, in coöperation with the American Chemical Society and the American Physical Society, should undertake the production and publication of Critical Tables of Chemical and Physical Constants. The American Chemical Society and the National Research Council mutually agreed to care for these two fields of chemical development. The American Chemical Society named as Trustees, to make the necessary arrangements for the publication of the monographs, Charles L. Parsons, Secretary of the American Chemical Society, Washington, D. C.; John E. Teeple, Treasurer of the American Chemical Society, New York City; and Professor Gellert Alleman of Swarthmore College. The Trustees have arranged for the publication of the American Chemical Society series of (a) Scientific and (b) Technologic Monographs by the Chemical Catalog Company of New York City.

The Council, acting through the Committee on National Policy of the American Chemical Society, appointed the editors, named at the close of this introduction, to have charge of securing authors, and of considering critically the manuscripts prepared. The editors of each series will endeavor to select topics which are of current interest and authors who are recognized as authorities in their respective fields. The list of monographs thus far secured appears in the publisher's own announcement elsewhere in this volume.

The development of knowledge in all branches of science, and especially in chemistry, has been so rapid during the last fifty years and the fields covered by this development have been so varied that it is difficult for any individual to keep in touch with

the progress in branches of science outside his own specialty. In spite of the facilities for the examination of the literature given by Chemical Abstracts and such compendia as Beilstein's Handbuch der Organischen Chemie, Richter's Lexikon, Ostwald's Lehrbuch der Allgemeinen Chemie, Abegg's and Gmelin-Kraut's Handbuch der Anorganischen Chemie and the English and French Dictionaries of Chemistry, it often takes a great deal of time to coördinate the knowledge available upon a single topic. Consequently when men who have spent years in the study of important subjects are willing to coördinate their knowledge and present it in concise, readable form, they perform a service of the highest value to their fellow chemists.

It was with a clear recognition of the usefulness of reviews of this character that a Committee of the American Chemical Society recommended the publication of the two series of monographs under the auspices of the Society.

Two rather distinct purposes are to be served by these monographs. The first purpose, whose fulfilment will probably render to chemists in general the most important service, is to present the knowledge available upon the chosen topic in a readable form, intelligible to those whose activities may be along a wholly different line. Many chemists fail to realize how closely their investigations may be connected with other work which on the surface appears far afield from their own. These monographs will enable such men to form closer contact with the work of chemists in other lines of research. The second purpose is to promote research in the branch of science covered by the monograph, by furnishing a well digested survey of the progress already made in that field and by pointing out directions in which investigation needs to be extended. To facilitate the attainment of this purpose, it is intended to include extended references to the literature, which will enable anyone interested to follow up the subject in more detail. If the literature is so voluminous that a complete bibliography is impracticable, a critical selection will be made of those papers which are most important.

The publication of these books marks a distinct departure in the policy of the American Chemical Society inasmuch as it is a serious attempt to found an American chemical literature without primary regard to commercial considerations. The success of the venture will depend in large part upon the measure of coöperation which can be secured in the preparation of books

dealing adequately with topics of general interest; it is earnestly hoped, therefore, that every member of the various organizations in the chemical and allied industries will recognize the importance of the enterprise and take sufficient interest to justify it.

Preface.

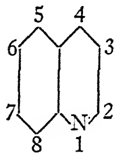
Since S. Fraenkel published the first edition of his classical work on synthetic drugs, *Arzneimittel-Synthese,* several books have been written in which the relation between chemical constitution and pharmacologic action has been discussed.

The present monograph is planned for the use of the research chemist and the pharmacologist as a guide through the literature of the quinoline derivatives. These include such outstanding compounds as Quinine, the Hydrocupreines, the Acridine Dyes, Plasmoquine, Cinchophen and Yatren (Chiniofon). Starting with quinoline, the nucleus common to all these compounds, the derivatives prepared by the introduction of certain groups are discussed, and the available pharmacological data of each new compound are collected. Among the great number of quinoline derivatives synthesized, only such compounds, however, are discussed which have been studied pharmacologically, or which are of clinical interest.

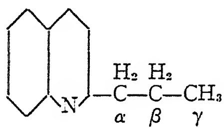
As far as possible it has been attempted to correlate the chemical constitution with the pharmacologic action, but, as a whole, the data available are too scanty to allow general conclusions. It is hoped, however, that the material offered in this book will assist the research chemist in his search for new compounds of a certain type and help the pharmacologist in the study of the pharmacologic action of similar compounds, or, if possible, to fill out the gaps in the existing material. For this reason it has been attempted to collect the pharmacologic literature as completely as possible. This will facilitate the repetition of experiments and at the same time will aid in the critical study of the material offered. The collection of the chemical data and references is less complete, because such data may easily be collected from the standard chemical works and from the patent literature.

In indicating the position of the different groups and radicles in the quinoline ring, in the aliphatic side chains, or in aromatic groups, the system used in *Chemical Abstracts* has been adopted.

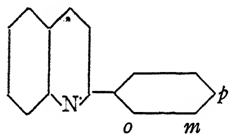
In indicating the position in the quinoline ring the following nomenclature is used:



In case of substitution in aliphatic side chains, Greek letters are used as follows:



Substitution in aromatic radicles connected with the quinoline ring is characterized by *o* (ortho), *m* (meta), and *p* (para):



In special cases the nomenclature will be explained in a footnote.

My especial thanks are due to Dr. T. Sollmann for his numerous suggestions and liberal advice, to Dr. H. P. Lankelma for the revision of the chemical sections, to Dr. M. S. Biskind for assistance in revising the text and to I. H. Marshall who assisted in reading the proofs.

W. F. von Oettingen

Cleveland, Ohio
December 1932

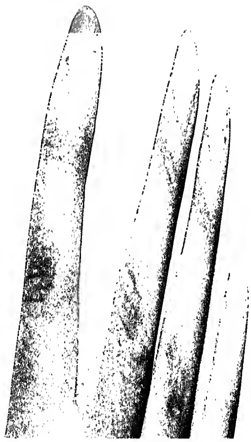
Table of Contents

List of Tables

List of Charts

Introduction.

About 300 years ago the use of cinchona bark was inaugurated as an antipyretic especially in malarial fever. In spite of every effort, the chemists of the entire world have not succeeded so far in replacing its active principle, quinine, by a synthetic drug of equal efficiency against malaria. Quinine and cinchonine are the most important alkaloids present in the cinchona bark and were first isolated by Pelletier and Caventou in 1820. During the remainder of the nineteenth century a number of other alkaloids were isolated as will be shown in the course of these pages. In 1842 Gerhard demonstrated that by fusing cinchonine with potassium hydroxide the quinine molecule can be decomposed; later it was found that aside from pyridine compounds, quinoline, 4-methyl quinoline, and other quinoline derivatives were thus formed. In this way the attention of chemists and clinicians was directed towards the study of the pharmacologic properties of quinoline and its derivatives. Since then numerous attempts have been made to synthesize compounds of antipyretic and antimalarial properties. As stated above, these efforts to discover a quinoline derivative as an adequate substitute for quinine, have so far not been successful. But in the course of these attempts a number of very valuable drugs, important in somewhat different directions, have been discovered, so that a review of the work achieved up to the present and a correlation of their pharmacologic action with their chemical constitution and their physico-chemical properties seem to be justified.

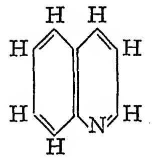


THE THERAPEUTIC AGENTS OF THE QUINOLINE GROUP

Chapter I.

Quinoline.

Quinoline,



was first isolated by A. Hoffmann (**1843**) from coal tar, but since it occurs there together with its homologs, it is difficult to obtain it in a state of absolute purity. The pure substance became easily available after Koenigs (**1879**), Baeyer (**1879**), Skraup (**1882**), and others had devised methods for its synthesis. It is a colorless, strongly refracting liquid of pungent odor, turning dark in contact with the air. It boils at 238° to 239° C. and has a specific gravity 1.095 at 20° C. The free base is not easily soluble in water, but is readily soluble in alcohol, ether and benzene; with equimolecular parts of acids it forms soluble salts. While the hydrochloride is hygroscopic, the tartrate is well defined and at the same time easily soluble in water. The characteristic salt, however, is the nearly insoluble bichromate with a melting point of 165° C. Other reactions are given in Rosenthaler, "Der Nachweis organischer Verbindungen," Stuttgart, Ferdinand Enke, Ed. II, p. 578.

Quinoline has marked *antiseptic* properties. Donath (**1881**), working with quinoline from coal tar, found that urine containing 0.2 per cent of quinoline did not turn putrid for weeks and that the drug interfered with a number of enzymatic processes. This antiseptic action, according to Rosenthal (**1888**), is so marked that animals poisoned with quinoline do not putrify for a long time. He stated that 0.75 per cent delayed the fermentation of yeast, recently confirmed by Niederehe (**1918**). This disagrees with Donath's report that even 5 per cent did not affect the fer-

mentation of yeast markedly; but in view of the considerable antiseptic properties it may be suspected that there may have been an error in Donath's experiments. Ameba and paramecia are killed in concentrations of less than 1 per cent and, according to Grethe (1896), concentrations of 1:1000 kill paramecia after approximately half-an-hour's contact. Niederehe (1918) found that solutions of 1:200 kill them within three to four minutes. Hata (1932) found that in concentrations of 1:100 quinoline kills streptococci in bouillon and in serum bouillon within fifteen minutes, being, however, less effective against *Staph. aureus* in the latter culture medium.

After oral administration of 0.2 gram per kilogram rabbit, McKendrick and Dewar (1875) observed progressive depression of the central nervous system with complete anesthesia, from which the animal recovered after from three to four hours. Larger doses of 0.25 to 0.3 gram per kilogram produced a comatose condition in which the animal died. This action concerns mostly the central nervous system. They considered the cardiac effect as secondary, due to asphyxia, and they observed also marked antipyretic effects. The peripheral nerves were said to have remained unaffected. R. Heinz (1890) confirmed these effects in rabbits, but he claimed that it also depressed the motor fibers. Stockman (1894) stated that the depression is followed by a period of increased reflex excitability, and that the peripheral motor paralysis occurs only with very large doses. Santesson and Koraen (1900) observed that with the administration of 0.2 gram per 50 grams frog, paralysis of the motor nerve endings occurs after fifteen minutes. The depressant effect on the central nervous system in fishes was studied by Jodlbauer and Salvendi (1905), who found that they became completely narcotized in from two to three minutes in concentrations of 1:800, while higher dilutions were less effective.

According to the observations of Santesson (1892) *striated muscle* is not affected by quinoline. The more susceptible *smooth muscle* of the intestine, according to Niederehe (1918), is stimulated by small concentrations (1:200,000) and depressed by greater concentrations (1:20,000). Stake (1929) found that it depresses the uterus and that it antagonizes the action of epinephrine but not that of barium chloride.

After the subcutaneous administration of from 0.2 to 1.0 gram to rabbits, Biach and Loimann (1881) and Stockman (1894)

observed collapse. Oschatz (1882) observed a cardiac depression in frogs. Fredericq and Terroine (1921) studied the effect of quinoline on the isolated heart of the tortoise. They found that concentrations down to from 5:1000 to 10:1000 cause a reduction of the heart rate, of the amplitude, and in large doses usually arrest in diastole. They also observed cardiac irregularities, characterized by extrasystoles with compensatory pauses, bigeminism and pulsus alternans. With smaller doses of 0.02 gram per kilogram rabbit, however, Niederehe (1918) observed no noticeable effect on the blood pressure nor on the amplitude or rate of the pulse. Kobert's (1884) observation that concentrations of 0.05 to 0.5 per thousand produce a moderate vasodilatation in perfused organs, was confirmed by Schuhmacher (1894), who found that this effect occurs first with the arteries and later with the veins. Both reports were recently confirmed and amplified by Stake (1929), who found that quinoline antagonizes and reverses the vasoconstriction produced by epinephrine; he concluded therefore that quinoline depresses the sympathetic motor nerve endings.

According to Schuhmacher (1894) quinoline dissolved in distilled water and in sodium chloride solutions in concentrations of one per cent and in doses of from 2 to 3 mg. per 35 grams frog has no effect on the motility of leukocytes. Shaw (1928) studied the mechanism of the absorption of quinoline and some of its derivatives by the blood cells and found that this is due to a true partition phenomenon, and not to adsorption or chemical combination.

The effect of quinoline on *respiration* varies with the dose used by different investigators. Donath (1881) stated that large doses depress the respiration. After subcutaneous administration of 0.3 gram Stockman (1894) observed slowing in rabbits and after 0.2 gram McKendrick and Dewar (1875) found a slight increase of the respiratory rate. Biach and Loimann (1881) used smaller doses and found no distinct effect in this regard. Thunberg (1913) found that quinoline markedly depresses the oxygen exchange of frog's muscle tissue.

Next to the antiseptic properties, the *antipyretic action* of quinoline and its derivatives aroused the greatest interest, as already noted by McKendrick and Dewar, and by Donath (1881). Donath found that 0.16 gram per kilogram, given subcutaneously to rabbits, reduced the temperature by one degree Centigrade,

larger doses being more effective. Similar results were reported by Biach and Loimann (1881) and Stockman (1894) after oral and subcutaneous administration of 0.1 gram per kilogram rabbit, the maximal effect being reached after one hour, with a slow return to the normal level. L. Brieger (1882) tried quinoline clinically as an antipyretic, but found that even 2.0 grams of the tartrate given three times daily had no marked effect on temperature, but produced undesirable side actions such as nausea and vomiting. After intravenous injection of 0.02 gram of quinoline per kilogram rabbit, Jess (1916) found severe changes of the retina, the lens remaining transparent.

The *fate* of quinoline in the organism has been studied by several investigators. Fühner (1906) believed that it is probably excreted as 5,6-dihydroxyquinoline bound to sulfuric or glucuronic acid. Scheunemann (1923) later isolated several compounds from the urine of rabbits which he described as 6-hydroxyquinoline, 8-hydroxyquinoline and 6-hydroxy-4-quinoline. Shizuaki (1924) noted that quinoline is also partly oxidized in the dog, and excreted conjugated with sulfuric or glucuronic acid. According to Kusui (1931) in the frog quinoline is converted into methylcompounds and partly oxidized (quinoline-quinaldine-quinaldinic acid).

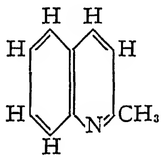
Quinoline is therefore a central depressant, with some curare-like action, and some depressant effect on the heart. It produces some vasodilatation and has little antipyretic effect. Its antiseptic action is fairly marked.

Chapter II.

Alkyl- and Aryl-substituted Quinoline Derivatives.

By introducing one methyl group into the quinoline ring seven isomers can be prepared, three of these being substituted in the pyridine and four in the benzene ring. Since the latter are prepared from *o, m,* and *p* toluidine by the Skraup method they are also called toluquinolines.

2-Methylquinoline, or **quinaldine,**



is a colorless liquid of quinoline-like odor, discovered in coal tar by Jacobson and Reimer (**1883**), and previously synthesized by Doebner and Miller (**1882**). It boils at 246° to 247° C. and is slightly soluble in water, but readily in alcohol, ether, benzene and acids, with the latter of which it forms salts easily soluble in water.

Its *antiseptic action* is less marked than that of quinoline. ✓ Grethe (**1896**) found that it kills paramecia in a concentration of 1:1000 within one-half to two hours, and Niederehe (**1918**) stated that the killing time is from three to four minutes in one per cent solutions.

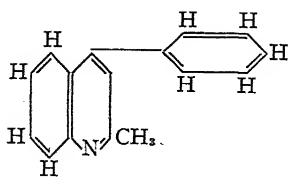
Stockman (**1894**) reported that the depressant action on the central nervous system and on the spinal cord is less marked than that of quinoline. A. Schmidt (**1884**) and Rosenhain (**1886**) observed similar symptoms; namely, depression, increase of pulse rate and of respiratory rate and abolition of corneal reflexes. They also observed collapse and failure of the circulation, but Niederehe (**1918**) noted that smaller doses, 0.01 gram per kilogram rabbit produce an increase of blood pressure of eight per cent (0.02 gram per kilogram—fourteen per cent) lasting for

several minutes, combined with a reduction of the pulse rate and amplitude. The same dose also increases the respiratory rate, and larger doses produce a less marked depression than corresponding doses of quinoline (Stockman, 1894). Fredericq and Terroine (1921) found that concentrations of 1: 1000 to 2.5: 1000 produce the same toxic effects as observed with quinoline, but that it is from four to five times more toxic than the mother substance. The concentration causing depression of the smooth muscle is the same as that of quinoline, namely 1:20,000, as reported by Niederehe (1918).

Cohn (1895) studied the fate of quinaldine in the organism by giving 1.5 grams twice daily to a dog up to a total dose of 21 grams. He found that it is evidently entirely decomposed in the organism. This agrees with A. Schmidt's statement (1884) that no cynurinic acid can be recovered from the urine after the administration of quinaldine. It should be mentioned that one of Cohn's dogs developed icterus on the third day, which disappeared on discontinuation of the drug, and Schmidt observed a general inflammation of the mucous membranes. He also found three per cent of sugar in the urine, indicating some hepatic (?) disturbance of the carbohydrate metabolism. The substance seems to be more toxic for rabbits than for dogs, as rabbits died with hemoglobinuria after a single subcutaneous injection of 0.7 gram; an abundance of hemoglobin casts were found in the kidney.

It appears, therefore, that introduction of one methyl group in the 2- position renders the compound physiologically less active as to the depressant action on the central nervous system, and more effective as to the circulatory action. The antiseptic properties are also reduced and the substance becomes less resistant to destruction in the organism.

4-Phenylquinaldine (2-methyl-4-phenylquinoline),



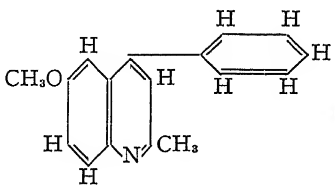
first prepared by Geigy and Koenigs (1885), consists of white platelets melting at 98° to 99° C., very slightly soluble in water, easily soluble in alcohol, ether, benzene and in acids with the for-

mation of salts. Of these the sulfate and dichromate are difficultly soluble. The acid solutions show blue fluorescence.

Grethe (**1896**) found its *antiseptic efficiency* much greater than that of quinoline and quinaldine, solutions of 1 : 1000 being immediately fatal for paramecia. Jodlbauer and Fuerbringer (**1897**) studied the pharmacologic properties more closely and observed that 0.03 gram in frogs produces restlessness, attended by slow and shallow respiration. Larger doses of 0.05 gram produce tonic and clonic convulsions, followed after twenty minutes by paralysis of respiration, the heart continuing to beat for some time. The same picture was seen in mammals. The cardiac action seems to be less marked, but there may be some rise of blood pressure and slowing of the heart after intravenous injection, presumably due to stimulation of the vasomotor and vagus centers. Solutions of 0.1 to 0.2 per cent produce hemolysis and enhance agglutination. Jodlbauer and Fuerbringer also found moderate *antipyretic action* in normal animals as well as in those suffering from heat-puncture fever. Mannaberg (**1897**) tested the antipyretic action clinically but found it too uncertain and too ineffective to warrant clinical use.

In comparing the action of this compound with that of quinaldine it appears that by introduction of the phenyl group in the 4- position the antiseptic qualities are increased considerably, the effect on the central nervous system is changed from depression to stimulation, very similar to phenol, which is perhaps split off in the organism.

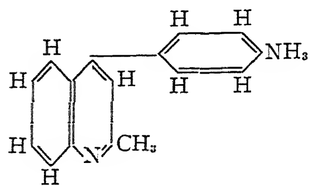
The corresponding 6-methoxy compound, **2-methyl-4-phenyl-6-methoxy-quinoline,**



first prepared by Koenigs and Jaeglé (**1895**), forms white platelets, melting at 76° C., easily soluble in alcohol, ether and acids. Dilute solutions of the salts show blue fluorescence. The melting point of the hydrochloride is 205° C. Grethe (**1896**) observed that paramecia are killed immediately in concentrations of 1 : 1000; in 1 : 10,000 and in 1 : 25,000 in four and five minutes respectively.

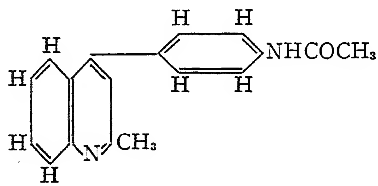
This compound is, therefore, somewhat more toxic than 2-methyl-4-phenyl-quinoline.

Introduction of an amino group in the *para* position in the phenyl ring yields **2-methyl-4-(p-aminophenyl)-quinoline,**



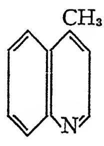
first prepared by Jellineck (**1886**). It consists of fine white needles, nearly insoluble in cold, fairly soluble in hot water, and easily soluble in alcohol, ether, chloroform and benzene. Grethe (**1896**) found that concentrations of 1:1000 killed paramecia immediately, 1:10,000 in eight minutes, and 1:25,000 in three hours, so that it appears that *introduction of an amino group into the phenyl ring reduces the toxicity slightly.*

The toxicity is still further reduced by introducing an acetyl group into the amino group. The **2-methyl-4-(p-acetylamino-phenyl)-quinoline**



kills paramecia in concentrations of 1:1000 in eight minutes, a dilution of 1:10,000 is not fatal. This marked decrease of the toxicity by the introduction of an acetyl group into the amino group is paralleled by the behavior of aniline and acetanilid.

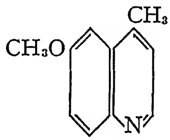
By introduction of a methyl group into the 4- position of the quinoline ring, **4-methylquinoline, lepidine,**



is formed. This compound was originally discovered in coal-tar, and can be prepared according to Koenigs and Mengel (**1904**); it is a colorless liquid which boils at 265.5° C. and has a specific

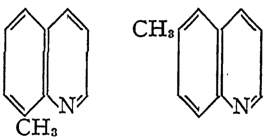
gravity of 1.0995 at 0° C. Although slightly soluble in water it is more soluble in alcohol, ether and benzene, and it forms water-soluble salts with acids. Its antiseptic action is about the same as that of quinaldine, concentrations of 1:1000 proving fatal in twenty-five minutes (Grethe, **1896**). In its pharmacologic properties it resembles quinaldine very much (Stockman, **1894**; Fredericq and Terroine, **1921**), and therefore, it appears that the position of the methyl group in the quinoline ring does not materially affect the pharmacologic action.

The corresponding methoxy compound, **4-methyl-6-methoxyquinoline,**



was also prepared by Koenigs. Grethe found it slightly more toxic than lepidine, as concentrations of 1:1000 kill paramecia in twenty minutes.

Methylation of quinoline in the benzene ring produces **8- and 6-methylquinoline,**

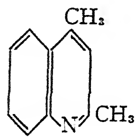


8– *6–*

both of which are prepared by the method of Skraup. Stockman (**1894**) studied both compounds and found no noticeable difference between the two nor between these two and those substituted in the pyridine ring. Cohn (**1895**), however, found the 8- compound more toxic than quinaldine, 0.7 gram subcutaneously injected producing a marked rigor of the muscle, progressive depression, paralysis and disappearance of reflexes after five hours. The respiration was slow and spasmodic while the heart action was not materially altered. The urine was rich in albumen and contained one per cent of sugar, which may indicate liver injury. A dog receiving one gram in a twenty per cent solution in olive oil twice daily, subcutaneously, showed no nervous symptoms, although he became very much emaciated. No 8-methylquinoline was recovered from the urine so that the substance is apparently completely oxidized in the organism. The 6-methylquinoline

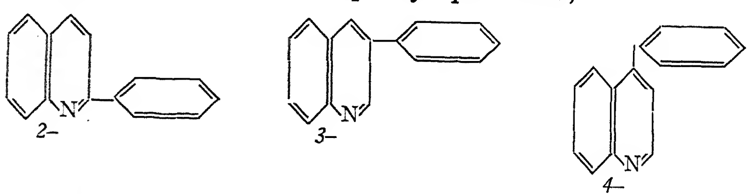
seems to be less toxic, because dogs stand the same dose without side action. This compound is also largely oxidized in the organism, and seven per cent of the injected material could be recovered from the urine in the form of 6-quinolinecarboxylic acid. 8-Methylquinoline was studied by Fredericq and Terroine (1921) in regard to its action on the isolated heart of the tortoise. It produces qualitatively the same effect as quinoline. It is, however, from four to five times more toxic than the latter, the minimal depressant concentration being 2.5 : 1000. On the other hand it was found to be slightly less toxic than the 2- and 4-methylquinolines.

By introducing two methyl groups into the quinoline ring **2,4-dimethylquinoline,**



is formed. This is a colorless liquid of specific gravity 1.0611 at 15° C., boiling at 264° to 265° C., and was first prepared by Baeyer (1879). The pharmacologic action was first studied by Stockman (1894), who found it to be less active than monomethyl quinolines. This observation confirms the assumption that *methylation reduces the toxicity of quinoline for the central nervous system.* As there are no statements on the fate of this compound in the organism, the question arises whether this decreased toxicity is paralleled by a greater lability towards oxidative processes in the organism as already observed with quinoline and quinaldine.

In contrast to the relatively low toxicity of methyl-substituted quinolines, the introduction of phenyl groups produces very toxic substances. The **2-, 3- and 4-phenyl quinolines,**



have been prepared by Friedlaender and Gehring (1883) and by Koenigs (1886). Tappeiner (1895), who studied their toxicity with paramecia, found that in concentrations of 1 : 10,000 the

toxicity is greater than that of quinine, the 2- compound being fatal in ten minutes, the 3- compound in three, and the 4- compound in from three to four minutes. These results agree with those communicated by Grethe (**1896**).

Kindt and Vollmer (**1930**) studied the pharmacologic action of series of β-naphtholquinoline compounds; namely, **β-naphtholquinoline, mono-nitro-β-naphtholquinoline, nitro-amino-β-naphtholquinoline, mono-amino-β-naphtholquinoline, diamino-β-naphtholquinoline, and phenantroline.** The minimal fatal dose of β-naphtholquinoline is 0.15 mg. per gram frog. The general toxic symptoms are central depression, disappearance of reflexes, muscular paralysis, hyperemia of the splanchnic area, cardiac arrest in systole and injury of the liver characterized by fatty infiltration. In regard to the cardiac action a disturbance of the conductivity seems to be of importance. In normal rabbits the intravenous injection of 50 mg. causes a fall of the temperature, dilatation of the pupils and dyspnea. The oral administration of 500 mg. causes essentially the same symptoms, at autopsy numerous hemorrhages in the vital organs were noticed. The substance has some antiseptic action because concentrations of 1 : 400 to 1 : 500 prevent putrefaction.

The hydrochloride of the **mononitro derivative** is so insoluble that it could not be studied pharmacologically.

The minimal fatal dose of the **nitro-amino-β-naphtholquinoline** is 0.21 mg. per gram frog and it is, therefore, less toxic than the unsubstituted compound, but qualitatively it acts very similar to the mother substance.

The minimal fatal dose of **mono-amino-β-naphtholquinoline** is 0.54 mg. per gram frog and that of the **diamino** compound 0.51 mg. Both compounds are considerably less toxic than the mother substance. The antiseptic properties are more marked, the concentrations preventing putrefaction being 1 : 600 and 1 : 1000 respectively.

It appears, therefore, that introduction of amino and nitro groups into β-naphtholquinoline reduces the toxicity in a way similar to the introduction of amino groups into the quinoline ring of cinchophen, and of 4-para-aminophenyl-2-methylquinoline.

Phenantroline was found to be more toxic than the β-naphtholquinoline, the minimal fatal dose being 0.11 mg., occasionally 0.17 mg. per gram frog. The central depressant action is less marked than with the β-naphthol quinolines, but phenantroline causes,

TABLE 1.—*Toxicity of Quinoline and Its Derivatives for Paramecia.*
(Time required to kill the organisms.)

Substance	Conc.	Time	Conc.	Time	Conc.	Time	Author
Quinoline	1 : 1000	½ Hr.	....	....	....	....	Grethe
	1 : 200	3-4 Min.	....	....	....	....	Niederehe
2-Methylquinoline (Quinaldine)	1 : 1000	½-2 Hrs.	....	....	....	....	Grethe
	1 : 100	3-4 Min.	....	....	....	....	Niederehe
2-Methyl-4-phenylquinoline	1 : 1000	Immed.	1 : 10 000	3-4 Min.	1 : 25 000	30 Min.	Grethe
2-Methyl-4-phenyl-6-methoxyquinoline	1 : 1000	Immed.	1 : 10 000	4 Min.	1 : 25 000	15 Min.	Grethe
2-Methyl-4-(p-aminophenyl)-quinoline	1 : 1000	Immed.	1 : 10 000	8 Min.	1 : 25 000	3 Hrs.	Grethe
2-Methyl-4-(p-acetylaminophenyl)-quinoline	1 : 1000	8 Min.	1 : 10 000	∞	....	....	Grethe
4-Methylquinoline (lepidine)	1 : 1000	25 Min.	....	....	....	....	Grethe
4-Methyl-6-ethoxyquinoline							
2-Phenylquinoline	1 : 1000	? 20 Min.	....	....	....	....	Grethe
	1 : 1000	1-2 Min.	1 : 10 000	10 Min.	....	....	Jodlbauer
3-Phenylquinoline	1 : 1000	½ Min.	1 : 10 000	3 Min.	1 : 25 000	15-30 Min.	Jodlbauer
4-Phenylquinoline	1 : 1000	8 Min.	1 : 10 000	3-4 Min.	1 : 25 000	4-6 Hrs.	Jodlbauer
Quinine	1 : 1000	3-4 Min.	1 : 10 000	2 Hrs.	1 : 25 000	∞	Jodlbauer

like the other compounds, muscular paralysis. With phenantroline the heart is also arrested in systole, but the effect on the conductivity is absent. It seems to have a direct depressant effect on the ventricular muscle. In concentrations of 1:200 it prevents the putrefaction.

From the data offered so far, it appears that introduction of one methyl group into the quinoline ring reduces the toxicity of the original compound for the central nervous system and increases it for the heart. The position of the methyl group in the quinoline ring seems to have little influence on the toxicity, the 2-, 4-, 6-, and 8-methyl quinolines have practically the same action, the 8- compound being perhaps somewhat more toxic than the others for the central nervous system but less so for the heart. Introduction of a second methyl group reduces further the pharmacologic effect. This is paralleled by similar changes in the phenyl group (phenol-cresol) and in the xanthine series (xanthine-caffeine).

Introduction of phenyl groups either in the quinoline or in the quinaldine ring increases the toxicity markedly and, at least in the case of 2-methylquinoline, changes the depressant into a stimulating action in its effect on the central nervous system. There are no data available in this series to indicate whether or not substitution in the phenyl ring would antagonize this convulsant action.

The toxicity of most of these compounds has been studied with paramecia and, therefore, these data allow a fairly good comparison.

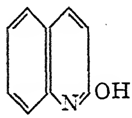
Table I gives a résumé of these results. The decrease of toxicity by the introduction of one or two methyl groups has already been discussed, as well as its increase by the introduction of phenyl groups. Introduction of an amino group into the para position of the phenyl ring tends to decrease the toxicity, which effect becomes more significant when this amino group is masked by acetylization. It should also be mentioned that introduction of a methoxy group into the 6- position of the quinoline ring, as in 2-methyl-4-phenyl-6-methoxyquinoline and in 4-methyl-6-methoxyquinoline does not produce a very significant change of the toxicity in the test tube experiment. Whether this, however, would also hold true in animal experimentation is another question.

Chapter III.

Hydroxy Derivatives of Quinoline.

Introduction of one hydroxy group into the quinoline ring produces compounds with the characteristics of bases and of phenols which, according to Filehne, give the cynurinic acid reaction of Jaffé.

2-Hydroxyquinoline, carbostyril,



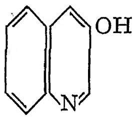
prepared by Friedlaender and Obermaier (1881) occurs in the form of white needles melting at 198° to 199° C. As a phenol of quinoline it has acid and basic characteristics and consequently it forms salts with both alkalies and acids; the former are, however, decomposed even by carbon dioxide.

Its *pharmacologic action* was studied by von Fenyvessy (1900). He found that from five to ten minutes after the subcutaneous injection of 0.25 to 0.3 gram per kilogram into rabbits, a progressive muscular weakness develops, and after half an hour this is very marked. The animals can be turned on their backs and show only weak defensive movements. As the reflexes are still present in this stage the action is not central. The respiration is first accelerated and then becomes slowed and difficult. There are no symptoms from the circulation other than a slight vasodilatation at the beginning, and the animals recover completely within from three to five hours. Except for hemorrhages in the fundus of the stomach, there are no characteristic post mortem findings, even after continued administration. In frogs the drug seems to produce a curare-like action. With local application to the rabbit cornea it produces marked inflammation lasting for several hours. Von Fenyvessy found that 2-hydroxyquinoline is excreted as conjugated glucuronic acid, and A. Schmidt (1884) assumed that it is bound to sulfuric acid. Rosenhain (1886) could not find any

cynurinic acid after the oral administration of 1 gram doses to rabbits. Binz and Räth (**1928**) found that the introduction of a hydroxy group in position -2- of quinoline-5-arsinic acid renders this substance parasitotropic for Nagana infections in mice.

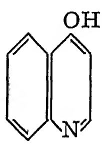
From these data it appears that introduction of a hydroxy group in the 2- position of the quinoline ring antagonizes the central depressant action of quinoline. It should be emphasized that no convulsant symptoms, as observed in the case of phenol, are reported.

Diasio (**1932**) reported on **3-hydroxyquinoline tartrate, termine,**



prepared by Schlauch (**1932**), which is said to be a powerful bactericide. Concentrations of 1:4000 kill *Staphylococcus aureus* in one-half to one second. It is said to be noncorrosive and non-irritant, to be little or non-toxic and to produce no changes of the tissue. The aqueous solution is slightly acid, having a pH 5.0. Clinically, used in form of foam-forming bougies, it gave in 90 per cent of 70 cases of gonorrheal urethritis anterior complete cure, the other 10 per cent being not of the anterior type. The treatment lasted for two to three weeks, was well tolerated and caused neither pain nor discomfort. Davin and Schlauch (**1932**) reported favorable results with this treatment in gonorrheal and nonspecific vaginitis, and Stein (**1932**) saw good results from its use in otitis.

The corresponding 4- compound, **4-hydroxyquinoline or cynurine,**

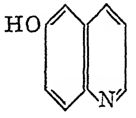


was prepared by Schmiedeberg and Schulten (**1872**) and consists of bright monoclinic prisms or needles melting at 52° C. After subcutaneous administration of 0.5 to 1.0 gram A. Schmidt (**1884**) observed no toxic symptoms in rabbits. After subcutaneous injection of 0.5 gram as a 10 per cent solution of the hydrochloride,

Rosenhain (1886), however, saw that in dogs general debility with slow recovery resulted. Apparently there is a possibility of its being less toxic than 2-hydroxyquinoline. It is excreted as conjugated glucuronic acid (A. Schmidt, 1884), which also holds true for the methoxy compound and for 4-oxyquinoline-2-carboxylic acid.

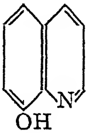
Introduction of one hydroxy group into the benzene ring yields 5-, 6-, 7- and 8-hydroxyquinoline; only two of these, the 6- and 8- compounds, have been studied pharmacologically. The latter is important as the starting material for a number of interesting compounds.

The **6-hydroxyquinoline,**



first prepared by Skraup (1883) forms white prisms melting at 193° C., is scarcely soluble in water, ether and benzene, and slightly soluble in alcohol. The antiseptic efficiency of this compound was found to be 300 times weaker than that of 8-hydroxyquinoline (Hata, 1932). Von Jacksch (1884) studied this compound as to its antipyretic action but after doses of 0.6 gram he observed only a slight decrease of the temperature, evidently without toxic symptoms. The corresponding methoxy compound was found to be even less effective, and the sulfate produced vomiting because of its acidity. Fredericq and Terroine (1921) studied its effect on the isolated heart of the tortoise. They found that it has the same inhibitory action as observed with quinoline and that it is more toxic than the latter but less so than the corresponding methyl compound.

The **8-hydroxyquinoline,**



can also be prepared by Skraup's method; it consists of fine needles melting at 75° C. It is scarcely soluble in cold water, slightly soluble in ether and more soluble in alcohol, acids and alkalies. The sulfate is the active principle of *quinosol,* in which it is mixed with potassium sulfate.

Quinosol.

The *antiseptic properties* of this compound have been much discussed. Hirschfelder and his co-workers (1923) found that it kills pneumococci in ten minutes in a concentration of 1 : 10,000, being less effective against streptococci, for which twice the concentration, namely 1 : 5000, is toxic in ten minutes. Browning and his co-workers (1922) found that it has marked antiseptic properties against *Staph. aureus,* but that it is only slightly antiseptic for *B. coli.* Hata (1932) reported that it is more effective against gram positive bacilli than against gram negative and sporeforming organisms. The corresponding ethoxy compound was found to be ineffective by Hirschfelder. Liese (1927) and Heubner (1926) consider it a good bacteriostatic agent, especially for *Staph. aureus* and streptococcus; less so, however, for *B. typhosus.* Van Winkle and Christiansen (1929) are of the same opinion. On the other hand, Krebs (1930) found that, at a pH 7.9, 10^{-2} mol of 8-hydroxyquinoline increase the proteolytic action of papaine 3.1 times. He believed that the heavy metals, which even in small quantities interfere with the action of papaine, form complex salts with hydroxyquinoline. R. Meier (1927) found that hydroxyquinoline affects the carbon dioxide formation of certain strains of yeast in concentrations which have no influence on the oxygen metabolism of the cells. In this respect it differs strikingly from phenol, which reduces the oxygen metabolism and increases the carbon dioxide formation. Hartung (1911) reported good results in the treatment of *Colitis contagiosa* with enemas of 100 to 200 cc. of a 0.25 to 0.5 per cent solution in normal saline, and Evers-Agnauer (1914) observed reduction of tenesmus and the number of stools in dysentery after oral administration of 150 cc. of a four per cent aqueous solution four times daily at intervals of one hour. Clinically it was found that 8-hydroxyquinoline favors the healing of inflammatory processes. Using the cantharidine blister method Haas (1932) found that after the administration of ten times 0.1 gram of quinosol in normal persons the response of the organism to inflammatory reactions was distinctly changed. The size of the blister and also the number of cells in the exudate was reduced with a relative increase of the number of lymphocytes, which may indicate an effect on the reticulo-endothelial system. Also Weichardt (1929) assumed that quinosol stimulates the defense mechanism of the

organism. He studied its effect on the formation of agglutinins in rabbits treated with typhoid vaccine and found that in the treated animals this occurred from two to three times more rapidly than in his control animals. The nontoxicity of the drug has been emphasized by the manufacturers of quinosol; but Heubner and Siegel (1926) found that the *toxicity* varies very much with the species, 0.1 gram per kilogram being non-toxic for guinea pigs and rabbits, one-third of this dose for cats, and one-fifth for mice. The toxic symptoms consist of excitement, sensory disturbances, depression, methemoglobin formation and increased excretion from the mucous membranes of nose and bronchi, producing dyspnea, and occasionally, even pulmonary congestion. Macht (1928) found that after injection of from one to five per cent solutions into the vagina, sufficient quantities are absorbed to produce tremors, spastic movements and stimulation of the respiration and circulation; larger doses produce depression and arrest of the heart. Heubner also found that subcutaneous injections produce necrosis of the skin. According to Van Winkle and Christiansen the susceptibility to such irritation varies very much with different individuals, and that this evidently depends less on the pH and on the acid radicle of the hydroxyquinoline compound, than on the chemical structure of the hydroxyquinoline itself.

Concerning its *fate* in the organism, Rost (1899) believed that it is excreted in the urine combined with sulfuric acid, and Brahm (1899) reported that it is bound to glucuronic acid. Grabbe (1928) found that it is rapidly absorbed from the intestinal tract and that in the middle third of the small intestine most of the drug is combined with acids. He states that it is excreted for the most part through the kidneys in the form of conjugated sulfuric acids and only in traces through the bile into the intestine, the excretion being completed in from twenty-four to thirty-six hours. He also found that in starving animals it increases the nitrogen metabolism, and that in such animals its excretion is slowed. In dogs, Boenheim (1914) found after the administration of 8-hydroxyquinoline an increase in the excretion of allantoin and a decrease in that of uric acid. The corresponding **salicylic acid ester (Aguttan)**, according to Brugsch and Wolfenstein (1915) depresses the uric acid formation and has been successfully used in gout. Boenheim (1914) found that small doses of 1.0 gram of the **hydroxyquinoline-acetylsalicylic acid ester** have no

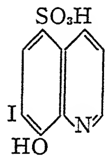
effect on the uric acid excretion, larger doses (5 grams) decrease the excretion of uric acid and increase that of allantoin. Larger doses (10 grams) also decrease the excretion of allantoin followed by a rapid increase, indicating a depression of uric acid formation. The **8-hydroxyquinoline glycerol ether** causes increase of the uric acid excretion and a decrease of that of allantoin. Seelkopf, Bender, Nahme and Schulze (**1932**) found that 8-hydroxyquinoline decreases the nitrogen content of the bile.

A mixture of 8-hydroxyquinoline sulfate and diphenyl-disazo-ethoxy-aminophenol-aminobenzoate of sodium is the urinary antiseptic **Ambazin** which was synthesized by Ebert. The diphenyl-disazo compound forms a yellow-brown colloidal solution and according to Rudnick (**1932**) is bacteriostatic and bactericidal for *Staph. aureus* in concentrations of 1:2000; but upon mixing with oxyquinoline sulfate the bacteriostatic action is said to be increased one hundred times the bactericidal properties being unchanged. The oral administration of 0.2 gram in capsules gave good clinical results in infections of the upper urinary tract with no side actions. Eighty-four to ninety-seven per cent of the dye is excreted with the urine in the first 48 hours.

In comparing the toxicity of the hydroxyquinolines with that of quinoline it appears that the former are less toxic; but in contrast to the methyl derivatives in this group of compounds, the position of the hydroxy group seems to be of importance. While the 6- and 4- compounds are but slightly toxic, producing no symptoms after doses of 0.5 to 1.0 gram, the 2- compound is distinctly toxic in doses of 0.25 to 0.3 gram per kilogram, or 0.5 to 0.6 gram per rabbit, and the 8- compound may produce toxic symptoms in even smaller doses. The type of action also seems to be different. The depression of the central nervous system is predominant with the 2- compound, and with the 8- compound a primary more or less marked stimulation may be observed. This difference may perhaps be due to the fact that in the first instance the hydroxy group is in the pyridine ring, and in the second in the benzene ring, resembling the phenols more in its character.

Yatren.

Among the derivatives of 8-hydroxyquinoline, **7-iodo-8-hydroxyquinoline-5-sulfonic acid,**



requires a more extensive discussion. This compound, mixed with sodium bicarbonate, is marketed under the names **Loretine, Yatren, Chiniofon and Anayodine.** It contains 28 per cent of iodine and is a microcrystalline powder, odorless and of sweetish taste, without a sharp melting point. On account of its content of sodium bicarbonate it forms sodium salts with the sulfonic acid radicle when moistened. In water it is soluble up to four per cent at ordinary temperatures, and in a larger proportion at temperatures between 60° and 80° C. It produces a green color with ferric chloride. The iodine is rather firmly fixed. Herzberg (1922) stated that the aqueous solution of a pure preparation of yatren requires boiling for fifteen minutes in order to liberate iodine. Other samples appear more easily decomposed by boiling. However, at room temperature iodine can be liberated only by oxidizing agents. Hachija (1927) found that boiling of the aqueous solution for half an hour increases the toxicity ten times especially in regard to liver injury. On the other hand, Schwartze and Billinghurst (1932) claimed that aqueous solutions of chiniofon liberate traces of iodine upon standing and that for cats the toxicity of the boiled and unboiled material is the same.

Table 2 is based on the publication of Bischoff (1913), Dietrich (1920), Arendt (1922), Herzberg (1922), and Breitenstein (1922). Bischoff's experiments show that the *antiseptic action* is very small although the bacteriostatic effect is distinctly greater. The results of Breitenstein were obtained with the silk thread method, and therefore are apt to be misleading. Chiba (1927) (quoted from Hata) found that yatren has a marked amebicidal effect *in vitro*. According to Hata (1932) yatren does not affect the growth of tissue cultures in a maximal concentration of 1:20,000, but concentrations of 1:125 are necessary to prevent the growth of contaminating bacteria.

The *toxicity* varies with different animal species and also with different individuals. Schuebel (1924) found the fatal dose for frogs to be 0.24 gram per kilogram, for mice 0.63 gram, for rats

TABLE 2.—*Antiseptic Action of Yatren on Different Organisms.*
(Concentrations required to kill within the time indicated.)

Author	Bischoff		Dietrich		Arendt		Herzberg		Breitenstein	
Organism	Conc.	Time	Conc.	Time	Conc.	Time	Conc.	Time	Conc.	Time
B. typhosus	1 : 20	35 Min.	1 : 200	3 Hrs.	....	....	....	....	1 : 40	6 Hrs.
Staphylococcus	1 : 10	35 Min.	1 : 40	3 Hrs.	....	....	1 : 100 water 1 : 33 serum	2 Min. 2 Min.	1 : 400	12 Hrs.
Streptococcus	....	....	1 : 40	3 Hrs.	....	....	....	....	1 : 10 000	12 Hrs.
Gonococcus	....	....	1 : 40	3 Hrs.	....	....	....	....	....	....
Pneumococcus	....	....	1 : 40	3 Hrs.	....	....	....	....	....	....
B. diphtheriae	....	....	1 : 200	3 Hrs.	....	....	....	....	....	....
B. Shiga	....	....	1 : 200	3 Hrs.	....	....	....	....	1 : 400	6 Hrs.
B. paratyph. aborti equi	....	....	....	....	1 : 20	3 Hrs.	....	....	....	....
Diplobact. capsul.	....	....	....	....	1 : 20	3 Hrs.	....	....	....	....
B. anthracis	....	....	....	....	....	....	....	....	1 : 25	48 Hrs.

0.6 gram, for guinea pigs 0.2 gram, for rabbits 0.2 to 0.4 gram, and for cats 0.36 gram. In cats he noticed fluorescence of the urine, albuminuria, and in several animals fatty degeneration of the liver. Zieler and Birnbaum (1922) reported two cases of atrophy of the liver after intravenous treatment with yatren; they therefore considered the intravenous administration dangerous and they believed that even oral administration may cause liver damage, so that careful control of the patients appears to be indicated. In two patients Michael (1922) observed that the intravenous injection of a five per cent solution that had been boiled for ten minutes produced severe toxic symptoms, characterized by loss of appetite, fatigue, nausea, vomiting and icterus; these disappeared after discontinuation of the drug. After intravenous injection Bauereisen (1921) observed irritation of the kidney. In the case of one patient suffering from dysentery Peter (1927) noted, twenty hours after the oral administration of 6.0 grams, urticaria, and swelling of the liver with excretion of urobilin in the urine. These symptoms disappeared after discontinuation of the drug. On the other hand, Eckert (1930) successfully treated with intravenous injections of five per cent yatren, a patient suffering from inoperable actinomycosis, administering 60 grams in the course of seven weeks. Towards the end of the treatment he gave as much as 100 and even 150 cc. at a time without seeing any toxic symptoms. It appears, therefore, that the toxicity of the drug is rather low, but that in certain conditions the treatment should be started with small doses of 0.5 cc., especially in chronic diseases which readily respond with violent reactions, as pointed out by Braun (1925).

The *pharmacologic action* was studied by Gessner (1929), who found that concentrations of 1:100 stimulate all parts of the intestinal tract; that this is characterized by an increase of tone and of rate, with a decrease of the amplitude of the contractions. Higher concentrations of from 1:100 to 1:20 produce a depression which can be antagonized by barium chloride. Schwartze and Billinghurst (1932) gave the stimulant concentration as 1:10,000 and the depressant as 1:300. Salamander larvae are not depressed by concentrations lower than 1:100 after ten hours; concentrations of 1:50 or 1:20 produce depression which is reversible by lavage with Ringer's solution. The toxicity for the isolated frog heart is very moderate, concentrations as high as 1:50 producing only a negative inotropic effect without disturb-

ing the frequency of the rate or the conductivity of the muscle. The effect on the blood picture was studied by Arbrink (1927), who found that intravenous injections of 14 milligrams per kilogram rabbit produced a marked thrombocytosis. It appears, therefore, that yatren stimulates the production of thrombocytes in the bone marrow and that it may act similarly on the lymphatic system. These findings may aid in the understanding of the therapeutic results obtained with the drug.

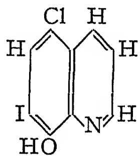
Under the assumption that yatren is not decomposed in the organism the *excretion* of yatren has been studied by determining the amount of iodine excreted. Nahme and Seelkopf (1932) gave in support of this assumption the following facts: (1) that the rate of the excretion of iodides is of a different type than that of yatren, and (2) that in blood mixtures no iodine is liberated at a pH above 1.0. Herzberg (1922) reported that after intravenous administration the drug is completely eliminated through the kidneys, both in normal and in sick individuals. But Nahme and Seelkopf (1932) found that after the intravenous administration to dogs noticeable quantities are excreted with the feces and that the ratio between urinary and fecal excretion evidently varies with the dose, which also affects the duration of the excretion. Herzberg claimed that the excretion is completed after from five and a half to six hours; but with oral administration only a fraction is excreted in the urine. In comparison with quinosol, Grabbe (1928) found the excretion greatly delayed by starvation, which was confirmed by Heubner (1929). Heubner found that in dogs the substance is very slowly excreted, and that a considerable fraction is excreted with the feces, which seems to be especially important in regard to its use in intestinal infections. From experiments of Nahme and Seelkopf (1932) it appears that yatren increases the carbohydrate metabolism and decreases the destruction of proteins. Jochmann (1926) studied both the distribution in the blood and the excretion by means of iodine determinations. He found that after intravenous administration of quantities corresponding to 154.5 mg. iodine, the normal iodine level is reached in the blood after four hours; with intramuscular injections into the gluteal region, after six hours. With intravenous injections the amount excreted in the urine after fifteen minutes was 43.6 per cent, and after four hours 91 per cent, so that it seems that the excretion is somewhat delayed with intramuscular injections. The reduction of the iodine level

in the blood runs fairly closely parallel with its excretion in the urine. Polyuria has no effect; oliguria produces first a decrease, later an increase of the excretion.

Although the antiseptic action of yatren is only moderate in test tube experiments, it has been extensively used as an antiseptic in the treatment of open wounds as well as in that of infected cavities and in general infections. There is an extensive literature on its clinical use along these lines. Since its action can hardly be direct it is probably indirect by stimulating in some way the natural defense mechanism of the organism. The extensive use of yatren in "Reizkoerpertherapy" is based on this assumption and there is hardly a pathologic condition in which it has not been used with reputed success. A priori it is difficult to conceive that a compound that is said not to be decomposed in the organism and which is completely excreted in from five and one-half to six hours, can produce such marked systemic reactions. But the effect of yatren on the thrombocytes, as demonstrated by Arbrink, and the observations of Freund (1920) on the rôle of thrombocytes in nonspecific protein therapy may lead to an understanding of this reaction. Zimmer (1926, quoted from Weicker) had claimed that also with oral administration yatren stimulates the self-defense mechanism. Weicker (1932) studied the effect of oral administration to normal rabbits and to rabbits with inflammatory processes caused by the subcutaneous injection of oil of turpentine. He found that it had only a moderate and inconstant effect in normal animals but that it caused a distinct leucocytosis in the diseased animals after a certain stage of the inflammation had been reached. It appears also possible that the sulfonic acid group in position 5- is responsible for the systemic action since Roehl (1926) and others have found that this group is liable to form compounds with proteins thus changing their physiological character. But the negative results of the experiments of von Oettingen and Ecker (1931) on the efficiency of yatren-albumen mixtures in preventing shock in animals sensitized to albumen, and vice versa, seems to exclude this possibility. According to Giemsa (1928) the amebicidal action of yatren is closely connected with the iodine atom in the quinoline ring. He reported that substitution of iodine by bromine or chlorine renders the new substances inactive in this respect but increases the irritant action on the intestinal tract which is especially marked in case of the chlorine derivative.

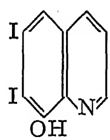
Gieserine is a double salt of 7-iodo-8-hydroxyquinoline-5-sulfonic acid, prepared by dissolving and warming equimolecular quantities of ammonium iodide and loretine. On cooling, the new compound is formed, which is said to be easily soluble in the stomach, but which has never gained much recognition.

Vioform, as a substitute for iodoform introduced by Tavel and Tomarkin (1900), is **5-chloro-7-iodo-8-hydroxyquinoline,**



representing yellow-brown needles, melting at 177° to 178° C. The alcoholic solution gives a green color with ferric chloride, similar to yatren. Its bacteriocidal and bacteriostatic action is greater than that of iodoform or loretine. Subcutaneous injections in rabbits of 0.1 to 0.3 gram per kilogram produce local irritation with abscess formation. As a wound antiseptic and dusting powder it is said to be at least equivalent to iodoform in efficiency.

Palm (1932) studied a **6,7-diiodo-8-hydroxyquinoline,**



as to its fate in the organism. This represents yellow needles which are insoluble in water but easily soluble in organic solvents. Theoretically it contains 64 per cent of iodine and the aqueous solution is said to be fairly stable. It is easily absorbed from the intestinal tract and mainly excreted with the urine in form of conjugated sulfuric and glucuronic acids. Only a small quantity remains in the organs. In the intestinal tract it is partly decomposed by the action of ferments and of bacteria. It is claimed that iodine is probably not split off during its passage through the organism.

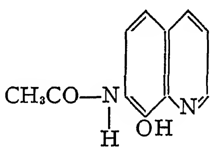
Other derivatives of 8-hydroxyquinoline which have been prepared and tried as antiseptics are **Chinaseptol, 8-hydroxyquinoline-7-sulfonic acid,** which according to Heubner (1929) causes in dogs an increased secretion of the urea nitrogen in normal

and a decrease in starved animals. Seelkopf and Nahme (1932) found that replacing the iodine in yatren by chlorine, **7-chloro-8-hydroxyquinoline-5-sulfonic acid,** does not change materially the effect on the protein metabolism. On the other hand introduction of a propyl-group in position -7-, 7-propyl-8-hydroxyquinoline-5-sulfonic acid, yields a substance which has no effect on the urinary nitrogen; whereas the unsubstituted quinoline-8-sulfonic acid causes an increase. It appears, therefore, that the quinoline ring as such is involved in this reaction, especially because analogous compounds of the aromatic series, **benzol sulfonic acid** and **p-phenolsulfonic acid** have no effect on the excretion of the urinary nitrogen (Nahme, 1932). According to the same author **guaiacol carboxylic acid** is only very little active in this respect, but the introduction of a propyl group, **propylguaiacolsulfonic acid,** increases the effect on the protein metabolism, i.e., quite the opposite effect as obtained by a similar chemical alteration in the quinoline series. According to Grabe (1932) the lithium salt of **8-hydroxyquinoline-7-carboxylic acid** increases the nitrogen excretion in the urine of dogs. There seems to be a marked difference between normal and starved animals inasmuch as the latter responds with a depression of the protein metabolism, similar as observed after the administration of hydroxyquinoline sulfonic acid. The corresponding acetyl ester behaves very similar as the unsubstituted compound so that it appears that the hydroxy group is not indispensable for this reaction. **Argentol** is the corresponding silver compound. **Oxychinaseptol or Diaphterine** is said to be a compound of o-phenolsulfonic acid with two molecules of 8-hydroxyquinoline. The hydroxy group of the latter is said to be linked to the sulfonic group of the o-phenolsulfonic acid. In regard to its antiseptic action Emmerich (1892) believed it equal to phenol, cresol and lysol. It is, however, scarcely toxic, for guinea pigs can stand the subcutaneous injection of 5 cc. of a 5 per cent solution or 15 cc. of a 1 per cent solution without noticeable toxic symptoms. Good clinical results were reported by Kronacher (1892) with 0.5 to 2.0 per cent solutions.

Anderson, David and Koch (1931) studied the relation of toxicity to amebicidal and balanticidal action of a series of hydroxyquinoline derivatives: **8-hydroxyquinoline; 8-hydroxyquinoline sulfate (Quinosol); 7-chloro-8-hydroxyquinoline;**

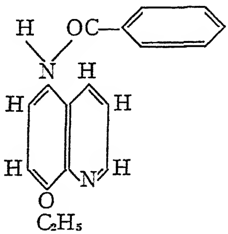
sodium-7-iodo-8-hydroxyquinoline-5-sulfonate (**Chiniofone**); **7-iodo-5-chloro-8-hydroxyquinoline** (**Vioform**); and a **diethyl-amino-dimethylene-hydroxy-iodo-chloro-quinoline hydrochloride.** They found that the toxicity increases with halogenization of hydroxy quinoline and in proportion to the atomic weight of the halogen. The further addition of solubilizing groups was found to decrease the toxicity of these compounds somewhat. The balanticidal action was found to increase with halogenization, but the amebicidal effect *in vitro* does not seem to be related in the same way with the chemical constitution of these drugs. **7-Allyl-8-hydroxyquinoline** reduces the urinary nitrogen in dogs. The minimal fatal dose is 2.3 to 3.0 grams per kilogram for mice and guinea pigs. Orally the latter stand 0.7 gram per kilogram and dogs 0.85 gram per kilogram without noticeable toxic effects.

Hata (1932) described a **7-acetamino-8-hydroxyquinoline,**



which consists of fine grayish needles insoluble in water but soluble in calculated quantities of acid and alkali. The acid solution is light brown and the alkaline solution has a green color. The sulfate, a grayish-white powder, is easily soluble in water. In the dry state this compound is relatively stable, but its aqueous solutions are easily decomposed. It is said to be about one-twentieth as toxic as 8-hydroxyquinoline and nearly non-irritant for mucous membranes. It is rapidly excreted with the urine, not hemotoxic, and in rabbits the intravenous injection causes leucocytosis which may last as long as three days. Hata found that its antiseptic action is greater in the presence of proteins than in their absence. Concentrations of 1:968,300 kill *Strept. hemol.* in serum bouillon, but in serum-free bouillon concentrations of 1:656,100 are required to do so. In animal experiments (mice) the minimal curative dose was found to be 1 cc. of a solution 1:400, whereas the maximal tolerated dose was 1 cc. of a 1:100 solution. The therapeutic index $\frac{\text{min. toxic dose}}{\text{min. therap. dose}}$ is, therefore, ¼.

Analgen, 5-benzoylamino-8-ethoxyquinoline,



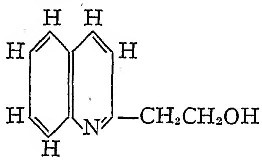
is another hydroxyquinoline derivative which has been used clinically for some time. It consists of a white powder, difficultly soluble in cold water and in alcohol, which melts at 208° C. In the stomach it is said to be split into 5-amino-8-ethoxyquinoline and benzoic acid. It was advocated as a urinary antiseptic, analgetic, and solvent for uric acid. According to Maas (**1895**) small doses produce depression of the central nervous system; large doses stimulate and then depress. It affects the reflex excitability, dilates the pupils and the peripheral blood vessels and causes death by arresting the circulation and the respiration. It has some cumulative action. Its decomposition product, 5-amino-8-ethoxyquinoline, produces first motor and then also sensory paralysis, and depresses the heart, in frogs. It is said to have some local anesthetic properties, presumably on account of the benzoyl group; but Hesse (**1930**) could not observe analgetic properties in mice. Analgen is said to decrease heat production and to act in this way as an antipyretic. Animals constantly fed with Analgen showed fatty degeneration of the liver. The therapeutic dose is 0.25 to 0.3 gram. Moncorvo (**1897**) believed it to be effective in malaria and in a number of nervous diseases as well as in gout and rheumatism. Characteristic after larger doses is the red color of the urine produced by the addition of acetic acid. The corresponding methoxy compound **5-acetamino-8-methoxy quinoline,** according to Freyss and Paira (quoted from Fraenkel) is physiologically inactive. The **dimethylcarbamic ester of 8-hydroxyquinoline** was studied by Aeschlimann and Reinert (**1931**). For mice the minimal fetal dose was found to be 150 mg. per kg. with intravenous and 400 mg. per kg. with oral administration. Five-tenths to one per cent solutions have a definite miotic action in cats. The corresponding quinolinium derivative, **dimethylcarbamic ester of 8-hydroxyquinolinium methyl sulfate,** is considerably more toxic, the

minimal fetal dose for mice being 0.5 mg. per kg. with intravenous and 200 mg. per kg. with oral administration. Concentrations of 0.25 to 0.5 per cent cause Definite miosis in cats lasting several hours, and concentrations of 0.2×10^{-5} cause a distinct contraction of the isolated rabbit intestine.

Sahashi (**1930**) studied the antineuritic properties of **2,6-dihydroxyquinoline** but found the curative value almost negligible. Seelkopf, Bender, Nahme and Schulze (**1932**) found that dihydroxyquinoline sulfate like hydroxyquinoline sulfate decreases the nitrogen content of the bile.

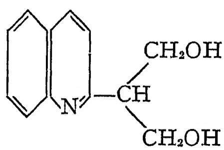
In the following, several quinoline derivatives will be discussed which have the hydroxy group in the side chain.

2(β-Hydroxyethyl)-quinoline,



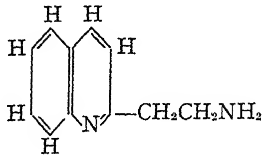
has been studied by Niederehe (**1918**). Its antiseptic action is less marked than that of quinaldine; concentrations of 1 : 100 kill paramecia in from 3 to 4 minutes, and the same holds true for its inhibitory action on the fermentation of yeast. Its effect on the circulation has been studied more closely. The changes of blood pressure are not constant; the pulse amplitude is somewhat increased, and with small doses the pulse rate is also increased; with larger doses, however, it is reduced. The compound has also a distinct vasomotor action, causing peripheral vasoconstriction. In the isolated rabbit intestine concentrations of 1 : 200,000 produce a slight stimulation; higher concentrations (1 : 20,000), depression of the intestine and of the isolated rabbit uterus.

2-(α,α-Hydroxyisopropyl) quinoline has a more marked vasomotor action (Niederehe, **1918**).



Kusui (**1931**) studied the fate of **2-quinoline propanediol** in the organism of the frog and found that it is not oxidized to the corresponding 2-quinoline carboxylic acid, which easily takes place *in vitro*.

The amine corresponding to the 2-(β-hydroxyethyl)quinoline, namely, **2-(β-aminoethyl)-quinoline,**



was prepared and studied by Loewe (**1918**), who found it relatively non-toxic in rabbits. With intravenous injection he observed a slight stimulation of the central nervous system. The drug depresses the isolated rabbit intestine, stimulates the guinea-pig uterus, and produces vasoconstriction. The pressor activity is a hundredth of that of epinephrine, but on the other hand its toxicity is a two-hundredth. Niederehe (**1918**) found that 0.001 gram per kilogram has no distinct effect on the blood pressure of rabbits, that twice this dose produces an increase of 40 per cent lasting for several minutes, and five times the dose produces a rise of 46 per cent followed by a slow decrease. The effect on the pulse amplitude is more marked, being 300 per cent with a simultaneous slowing of the rate of 34 per cent. The intensity of its action with regard to the rise of blood pressure is said to be one-fortieth, its vasoconstrictor action one twenty-fifth of that of epinephrine. The depressant effect on the isolated rabbit intestine is distinct in concentrations of from 1:2,000,000 to 1:300,000 and is, therefore, ten times more effective than quinoline-α-ethanol. The minimal fatal dose for the mouse is 0.62 mg. per kg.; toxic doses produce a primary stimulation, followed by depression of the central nervous system. Its antiseptic action, measured by the inhibition of the fermentation of yeast, ranges between that of quinaldine and quinoline; in concentrations of 1:666 it kills paramecia in from three to four minutes.

The corresponding **4-hydroxynaphthyl compound,** also studied by Niederehe, shows generally the same reactions, although weaker. From this it appears that the vasomotor action of 2-(β-aminoethyl)-quinoline is largely due to the aminoethyl group in the side chain, and the question arises whether an unsubstituted aminoethylnaphthyl would not have even more striking similarities.

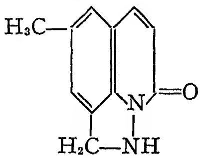
Since a great number of the compounds mentioned in this group have not been studied extensively as to their pharmaco-

logic action, but rather within the scope of a certain question, it is difficult to evaluate the relation between chemical constitution and pharmacologic action. The 2-hydroxyquinoline produces some depression of the central nervous system, irregularities of the cardiac action and a moderate vasodilatation and, therefore, does not differ markedly from quinoline. The 4- compound seems to be less toxic, and the same holds true for the 6- compound. The latter has some antiseptic action which is almost lost by masking the hydroxy group with a methyl group. The 8-hydroxy compound produces some stimulation of the central nervous system, passing later into depression, and differs in this respect from the other compounds of this group. This action seems to be antagonized by the introduction of halogens and sulfuric acid groups.

Introduction of hydroxy groups into the side chain yields compounds with a moderate systemic action but with distinct vasoconstrictor qualities. This is more marked, however, with the corresponding amine, and, as pointed out, it is obvious that this is an effect of the alkylamine group rather than of the quinoline radicle. The antiseptic action of the hydroxyquinolines seems to be moderate as compared with that of other alcohols, for instance the phenols, but that they influence the metabolism and stimulate the self-defense mechanism after oral and intravenous administration.

Cytisine, $C_{11}H_{14}N_2O$, is an alkaloid which has been isolated from several papilionaceae, it is the toxic agent of *Cytisus laburnum,* the seeds of which may contain 1.5 per cent of the alkaloid. It was first isolated in pure form by Husemann and Marmé (**1865**) and is identical with ulexine, sophorine and baptitoxine.

Cytisine crystallizes in crystals which melt at 152° C. and are easily soluble in water, alcohol and chloroform and less in ether. It is levorotatory. The solutions have a bitter taste and are of strongly alkaline reaction. The chemical structure has been studied by Ewins (**1913**) and Spaeth (**1919**), who assigns to cytisine the following formula,



and, therefore, it may be considered as a derivative of 2-hydroxyquinoline, although pharmacologically it resembles closely nicotine.

It is readily *absorbed* from the intestinal tract and is mostly *excreted* with the urine, partly also with the saliva and the milk. The latter may, therefore, cause poisoning as reported in the literature after feeding to an infant the milk of a goat which had eaten the leaves of cytisus (Kobert, 1890).

The *central nervous system* is first stimulated and later depressed. Prevot and Binet (1887) stated that small doses which are else ineffective may cause vomiting due to central stimulation. According to Marmé (1887) this stimulation extends also to other medullary centers and with sufficiently large doses this stimulation may be followed by depression (Radziwillowicz, 1888). According to Fuehner and Mertens (1921) it resembles nicotine in its central action.

The *peripheral motor nerves* are depressed and evidently also the sensory fibers (Radziwillowicz, 1888) and according to Dale and Laidlaw (1912) the ganglia are first stimulated and later depressed. Already the first observers (Prevot and Binet, 1887; Bradford, 1887; Radziwillowicz, 1888) had noticed that cytisine has "curare action" paralyzing the receptive mechanism in the striated muscle. As Fuehner and Mertens (1921) pointed out, it differs in this respect from nicotine with which this action is absent. Although it increases like nicotine the tone of the plexus-free leech preparation it is from one-half to one-third less effective, and it does not cause the characteristic nicotine position in the frog.

Large doses affect also the *circulation*. Already Prevot and Binet (1887) stated that with large doses frogs die from paralysis of the heart. According to Marmé (1887) and Bradford (1887) small doses cause a short rise of the blood pressure due to peripheral vasoconstriction. Kraepelin (1887) utilized clinically the vasomotor action in patients suffering from hemicrania and melancholia. Depending upon the dose and upon the vasomotor effect cytisine may increase or decrease the urinary excretion. Bradford was especially impressed by the diuretic action and suggested the use of cytisine for this purpose.

The *toxicity* of cytisine varies with different species. Already Prevot and Binet pointed out that dogs, cats and pigeons are much more sensitive than rabbits and according to Radziwillowicz the cat is forty times more sensitive than the goat but only three times more susceptible than the chicken. Poisonings with cytisine are not infrequent, especially with children. The symptoms are vomit-

ing, diarrhea, prostration and depression which may or may not be preceded by excitement. On account of the violent vomiting caused by the drug fatal poisonings are rare, and Radziwillowicz reported only five fatalities among 131 cases of cytisine poisoning.

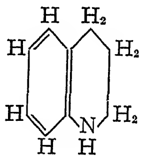
Chapter IV.

Hydrogenation Products of Quinoline.

Originally Skraup and other chemists considered quinine to be a tetra-hydroquinoline derivative and for this reason the hydroquinolines early aroused the interest of chemists and clinicians. Besides, experiences with other substances such as pyridine and piperidine showed that hydrogenation of the double bond renders the new substance more effective in the organism. Depending on the degree of hydrogenation, several compounds, namely dihydroquinoline, tetrahydroquinoline, hexahydroquinoline, and decahydroquinoline and their derivatives have been prepared.

Dihydroquinoline has not been studied pharmacologically, but Rehns (1901) reported that the one derivative studied proved to be very slightly toxic as compared with tetrahydroquinoline, especially concerning the pathologic changes in the kidney.

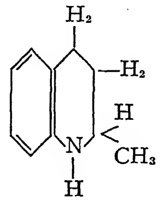
Tetrahydroquinoline,



first prepared by Wyschnegradsky (1879) and later by Bamberger and Lengfeld (1890) is a colorless liquid at ordinary temperature, boiling at 244° C. Rosenhain (1886) found that 8 grams injected subcutaneously into rabbits produced a gradually increasing depression, so that the animals died within thirty-six hours. The urine of these animals contained albumen and blood coagula were found in the calices of the kidneys. The compound could be partly recovered from the urine. Similar kidney changes were reported by Rehns (1901). He observed a bilateral necrosis of the renal papillae in two to three days after the subcutaneous injection of 2 cc. of a one per cent solution of the hydrochloride into guinea pigs. Fredericq and Terroine (1921) found that concentrations of from 2.5 : 1000 to 5 : 1000 have the same depressant action on the isolated heart of the tortoise as quinoline

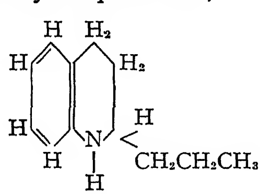
in concentrations of from 5 : 1000 to 10 : 1000, being in this respect, therefore, more toxic than the mother substance.

Tetrahydroquinaldine,



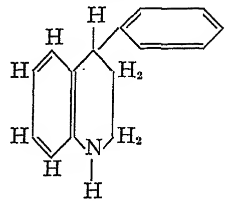
is, according to Jackson (1881), a colorless oil of sweetish odor, boiling at 243° to 246° C. It contains one asymmetric carbon atom, and, therefore, forms isomers which can be separated by means of their bitartrates and α-bromo camphor sulfonates into optically active nitrogen compounds. Both isomers were studied by Dale and Mines (1911). They found that 0.0005 molar solutions of the hydrochloride produced diastolic arrest of the frog heart, probably due to electrolytic dissociation of the salt, the tetrahydroquinaldine being only a weak base. Neutral solutions in concentrations of 0.001 mol produced only a slowing of the heart; in this respect there was no difference between the two isomers. On striated muscle 0.01 molar solutions produced shortening and loss of excitability. The effects were more marked with the levo- than with the dextro-rotatory compound, the former being about one and one-half times more toxic.

The 2-propyl-tetrahydroquinoline,



is a liquid that boils at 258° C. Plugge (1897) found that in frogs it produces a paralysis of the central nervous system and also of the peripheral nerve endings, the former effect being, however, more marked. It also depresses the frog heart, producing diastolic arrest. Although it is quite toxic for paramecia, Plugge considered it to be comparatively non-toxic for mammals. In this respect it differs markedly from the corresponding 2-propylpiperdine which is from ten to twelve times more toxic for mammals and practically non-toxic for infusoria.

4-Phenyl-tetrahydroquinoline,

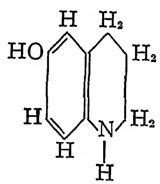


according to Koenigs and Meimberg (**1895**), forms bright leaflets, melting at 74° C. The hydrochloride occurs as long needles easily soluble in water and in alcohol. Grethe (**1896**) studied this compound in regard to its toxicity for paramecia, and found that concentrations of 1 : 3000 kill the paramecia in three, 1 : 5000 in eight and 1 : 10,000 in fifteen minutes. A comparison of these values with those obtained with phenylquinoline reveals that the toxicity for paramecia is decreased by hydrogenation.

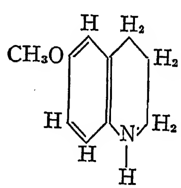
Thalline.

The hydroxy derivatives of tetrahydroquinoline are important because some of their derivatives have been used as antipyretics:

6-Hydroxy-tetrahydroquinoline,



prepared by Skraup (**1883**), was studied by von Jacksch (**1884**), who found it to be very toxic, because doses of 0.2 to 0.6 gram proved fatal for rabbits in two hours, and the animals died with clonic convulsions. The corresponding methoxy compound, **Thalline,**



was also prepared by Skraup (**1883**). It consists of thick prisms melting at 42° to 43° C. The free base is difficultly volatile with

steam and scarcely soluble in water; it is more soluble in alcohol, ether and benzene. The hydrochloride and the sulfate form well-defined crystals which are soluble in water, their aqueous solution being of acid reaction.

The *antiseptic action* seems to be reduced as compared with that of the 6-methoxy lepidine, for Grethe (**1896**) found that concentrations of 1 : 1000 kill paramecia only after one and one-half hours. Similar results were reported by Engel, but Bokorny (**1892**) stated that 0.02 per cent solutions depress the fermentation of yeast in twenty-four hours.

With regard to its *fate* in the organism, Blumenthal (**1885**) reported that only a part of the thalline passes through the organism unchanged, and the decomposition products were held responsible for the greenish-brown color of the urine after its administration. Kumagawa (**1888**) fed 9.5 grams of the sulfate to a dog, which resulted in an increased nitrogen metabolism.

Von Jacksch found that 0.6 gram of thalline can be given to rabbits without producing marked toxic symptoms, and that it has considerable *antipyretic properties*. According to Feri (**1911**) the subcutaneous administration of 0.15 gram to rabbits reduces the temperature in coli fever 1.6° C. for one hour and fifteen minutes. Ehrlich (**1886**) found that 0.03 gram per kilogram rabbit produces a fall of temperature which becomes more marked by increasing the dose; the maximal therapeutic effect being produced with a dose of 0.1 gram, which quantity cannot be increased without manifestation of toxic symptoms. For this reason he also suggested starting clinically with small doses given at short intervals until the minimal effective dose has been determined for each patient. With other methods of administration undesirable side actions may become very marked. Falk (**1890**) pointed out that the antipyretic action of thalline is associated with a profuse perspiration beginning in from ten to fifteen minutes after the administration, and lasting for a considerable time. During this period the skin may show first a marked erythema, which later changes to a cyanotic color. He reported that not infrequently marked paroxysms may be observed, followed by a rapid rise of temperature. Ehrlich (**1887**) observed with large doses very marked muscular tremor, trismus and salivation. The cyanosis and the cardiac disturbances indicate the toxic action on the circulatory system, which may be due partly to methemoglobin formation, observed by Brouadel (**1889**) and Robin (**1889**). Aside

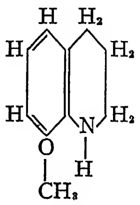
from this effect on the blood the latter found also a depressant action on the central nervous system. For these reasons, and on account of gastrointestinal disturbances, which are also observed after the administration of the drug, its clinical use has been discontinued.

According to Hesse (1930) thalline in non-toxic doses has slight analgetic properties. Schuhmacher (1894) observed that it does not affect the motility of leucocytes, and that it differs in this respect from quinine.

Santesson and Koraen (1900) found, aside from its depressant action on the central nervous system, also a distinct curare-like action on the peripheral motor nerve endings, this effect being twice as marked as with quinoline, which may be due to hydrogenation of the quinoline nitrogen. Fredericq and Terroine (1921) found that in concentrations of 1 : 1000 to 2.5 : 1000 it depresses the isolated heart of the tortoise in the same way as observed with quinoline and tetrahydroquinoline, the depressant concentrations of which are 5 : 1000 to 10 : 1000 and 2.5 : 1000 to 5 : 1000 respectively. The introduction of the methoxy group in the quinoline ring, therefore, shifts the toxicity for the heart in the opposite direction than does the substitution in the quinine series.

Ehrlich (1886) had pointed out that thallium produces fatty degeneration of different organs and especially of the kidney. This was confirmed by Rehns (1901), who found that after the administration of 0.1 gram in guinea pigs fatty degeneration of the kidney takes place after two to three days, and even sooner. Mice and rats are said to be less susceptible.

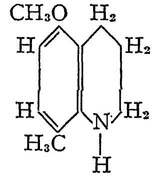
Ortho-thalline (8-methoxyquinoline),



was prepared by Ehrlich (1886) by the Skraup method, but it was found to be more toxic than the 6- compound, especially in that it has more caustic effects. The antipyretic action is less marked, 0.05 gram per kilogram showing practically no antipyretic action. Higher doses seem to be more effective in this

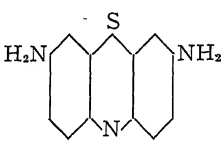
respect, but are of no therapeutic value because of the marked toxicity. This compound also produces degenerative changes in the kidney, as found by Rehns (**1901**), 0.05 gram proving fatal to guinea pigs within twenty-four hours.

The **5-methoxy-8-methyl-tetrahydroquinoline, anathalline,**



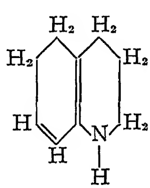
was also studied by Ehrlich (**1886**) but was found to have only very slight antipyretic action, and, although the undesirable side actions were less marked than with thalline, it was found to be of no therapeutic value. It may produce degenerative changes in the kidney (Rehns, **1901**).

From this it appears that the 6- position of the methoxy group is the most favorable for the antipyretic action, which accords with the fact that in dyestuff chemistry the radicles in this position are frequently the chromophorous groups and are responsible for salt formation. Ehrlich found that the affinity for nervous tissue is also favored by groups in the 6- position, because thionine



stains nerve endings very well whereas the jo-thionine, which contains both amino groups in one benzene ring, has no staining qualities for nervous tissue.

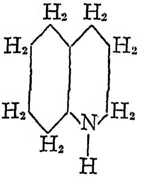
The **hexahydroquinoline,**



prepared by Bamberger and Lengfeld (**1890**) is a viscous, water-clear oil, which turns brown readily when exposed to the air, and boils at 226° C. It is slightly soluble in water, easily soluble in

organic solvents and in acids. The hydrochloride forms glistening white needles melting at 170° C. Heinz (1890) found that it resembles quinoline in regard to its cardiac and central action, but that it is more toxic as a blood poison.

Decahydroquinoline,



was also prepared by Bamberger and Lengfeld (1890). It consists of white needles melting at 48.2° to 48.5° C. and boiling at 204° C. It has a strong odor, is volatile with steam and forms salts with acids. The hydrochloride forms colorless rhombic platelets which are freely soluble in water. According to Heinz (1890) its pharmacologic action greatly resembles piperidine in regard to its effect on the central nervous system; it affects the circulation less than quinoline but its toxic action on the erythrocytes is by far the most marked among all the hydrogenated quinoline derivatives.

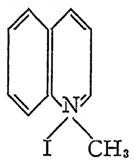
In summarizing these results it appears that the toxicity for the central nervous system is decreased by hydrogenation, as has been shown by Trendelenburg (1912) for santonin and tetrahydro-santonin, the latter having a distinctly less marked convulsant action. The toxic effect on the erythrocytes and on other organs, especially on the kidney, however, is markedly increased. On the other hand, von Jacksch reported no toxic symptoms after the administration of 0.6 gram of 6-hydroxyquinoline, whereas with 0.2 to 0.6 gram of the 6-hydroxy-tetrahydroquinoline, he observed fatal convulsions, so that in this instance the effect on the central nervous system also seems to have been increased.

Chapter V.

Quaternary Bases of Quinoline.

By adding alkyl radicles to the nitrogen atom of the quinoline ring, quaternary ammonium bases are formed, which have a specific property in common. Brown and Fraser (1868) found that the methyl and ethyl compounds of certain alkaloids, obtained by interaction of methyl and ethyl iodide respectively, paralyze the peripheral motor nerve endings. Jolyet and Cahours (1868) pointed out that this was also the case with methyl, ethyl, and amyl aniline. Brunton and Cash (1883) and Rabuteau (1884) observed the same phenomenon with tetra-methyl- and tetra-ethyl ammonium iodide and Bochefontaine (1882) with oxyethyl-quinolinium chloride. It is now recognized that this "curare" action is a general property of most quaternary ammonium bases.

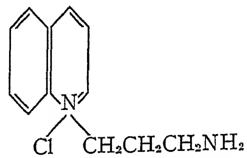
McKendrick and Dewar (1875) studied the properties of **methyl-, ethyl-, and amylquinolinium,**



obtained by heating quinoline with the corresponding iodides in a sealed tube. The hydroiodide and the sulfate were used for these experiments, the former being slightly more active. The action of the methyl quinolinium greatly resembles quinoline, but the tendency to produce spasm was said to be greater, and to be even more marked with the higher homologs, ethyl- and amyl-quinolinium. They noted, however, a contrast with the higher bases of quinoline, lepidine, etc., which do not produce such complete unconsciousness but are attended by twitchings, muscular tremors and even opisthotonus, indicating irritation of the motor centers. They do not state whether these compounds have a curare-like action, but Santesson and Koraen (1900) found that the methylquinolinium chloride has a marked curare-like action on the motor nerve endings of the frog. Similar observations

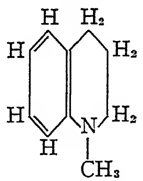
were made by Stockman (1894) with methylquinolinium iodide and methylisoquinolinium iodide, both showing the phenomenon to a considerable degree.

β-Aminoethyl-quinolinium chloride

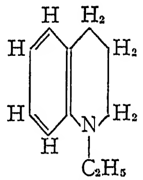


was studied by Loewe (1918), who found it to be much more toxic than the corresponding C-substituted compound as to its paralyzing action, although its effect on the isolated intestine, the blood vessels and the uterus were less marked. Unfortunately an analysis of the paralyzing action was not made, but the fact that the paralyzed animals remained conscious may indicate a peripheral curare-like action.

Filehne had come to the conclusion that only N alkyl substituted quinoline derivatives would yield promising antipyretics. The first compounds synthesized in this direction by Hoffmann and Koenigs (1883) were **1-ethyl-tetrahydroquinoline, Kairoline A,** and **1-methyl-tetrahydroquinoline, Kairoline M.**



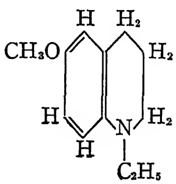
Kairoline M



Kairoline A

The Kairoline A was studied by Filehne (1883) as to antipyretic action; although this was rather marked it has never been used clinically, because more promising antipyretics were synthesized. Later Rehns (1901) observed that it has the nephrotoxic properties similar to those of thalline.

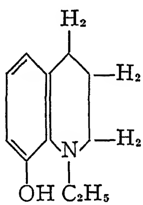
Introduction of an ethyl group into the nitrogen of the thalline molecule yields **ethyl thalline,**



which was first prepared by Skraup (**1882**). It is a viscous oil boiling at 287° to 287.5° C., and forms salts with acids. Of these salts the hydrochloride consists of white platelets which are very soluble in water. Von Jacksch found in rabbits that 0.6 gram produced a very noticeable fall of temperature without being markedly toxic.

KAIRINE.

Introduction of a hydroxy group in the 8- position of the Kairoline molecule yields **1-ethyl-8-hydroxy-tetrahydroquinoline, Kairine A or Kairine,**



which was first prepared by O. Fischer (**1884**) and which consists of white monoclinic platelets, melting at 76° C. The free base is nearly insoluble in water, but forms salts with acids and with alkalies. The aqueous solutions of these salts give a purple color with ferric chloride, which turns into a dirty brown on standing.

According to Fr. Mueller its *antiseptic properties* are moderate as compared with those of quinine and salicylic acid, when tested as to its effect on the fermentation of yeast and as antiseptic against molds.

Von Mering (**1884**) and Schmidt (**1884**) found that it is excreted in the urine as conjugated sulfuric acid, the excretion being complete after twenty-four to thirty-six hours. After the administration of kairine the urine shows a characteristic green color.

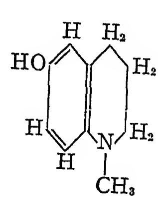
As to the *toxicity* of this compound, Schmidt (**1884**) observed muscular twitchings in rabbits after the administration of 1 gram. These were followed by marked depression from which the animals recovered only after several hours. He also noted marked secretion from the mucosae, and increased flow of saliva and tears, symptoms which were also observed by Heubner (**1926**)

in his studies on the toxicity of 8-hydroxy quinoline. The animals usually died within twenty-four hours. The urine contained hemoglobin and some albumen, while epithelial casts and decomposed blood were found in the kidney, although Rehns (1901) reported the kidney changes less severe than with thalline.

The mechanism of the kairine *antipyresis* was studied by Krehl and Matthes (1897). They found that in rabbits doses of 0.01 gram markedly lowered the temperature of infectious fevers by reducing the heat formation. Richter (1891) observed that increased heat dissipation is also involved in the antipyretic action of kairine; this was confirmed by Stuehlinger (1899) in the case of rabbits suffering from pyocyaneus fever. Since Thomson (1886) observed vasodilatation in organs perfused with concentrations of 0.5 to 1:1000, Stuehlinger's assumption seems to be supported.

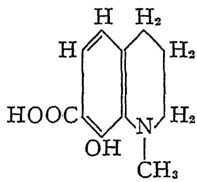
Filehne (1882) and Merkel (1884) considered kairine clinically a good antipyretic and Guttmann (1883) pointed out that its action, although less prolonged, is quicker than that of quinine, and that repeated small doses totalling three to four grams per day produce a more complete and more uniform reduction of the temperature than does quinine. Other clinicians, *cf.* Riess (1883), considered it inferior to other antipyretics such as salicylic acid; it was also emphasized that the administration of kairine was not infrequently followed by chills, collapse and cyanosis. The latter is probably due to the formation of methemoglobin as observed by Kobert (1887) after kairine. It has been claimed that kairine has some analgetic properties, but this was denied by von Mering (1884) and more recently by Hesse (1930). Because of the side actions mentioned above the clinical use of the drug has been discontinued.

After von Mering had found that in thalline the antipyretic action depends largely on the introduction of the methoxy group in the 6- position, Ehrlich (1886) synthesized a **6-hydroxy-kairine,**



but found the substance very toxic and extremely irritant. From this he concluded that the irritant action of these compounds is due to the hydroxy group rather than to the lability of the hydrogen attached to the quinoline nitrogen, as assumed by Filehne.

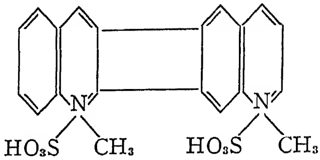
Another attempt to prepare an antipyretic from quinoline is the synthesis of **1-methyl-8-hydroxytetrahydroquinoline-7-carboxylic acid,**



which may be termed the 7-carboxylic acid of kairine M, prepared by Demme (**1888**). This is a well-crystallized compound which forms soluble salts with mineral acids. According to Demme 1 gram in frogs produces, after five minutes, increased systolic contraction of the heart followed by slowing, cardiac irregularities, and diastolic arrest, and in ten to fifteen minutes after the injection tetanic convulsions are observed which are followed by paralysis. In the case of rabbits, subcutaneous administration of 1.0 to 1.5 grams produces rise of blood pressure and slowing of the heart, while repeated doses of 0.25 gram produce muscular twitchings and convulsions. In normal animals no antipyretic action is observed. Clinically 0.1 to 0.25 gram three to four times daily produces a moderate antipyretic action, but the effect is evidently not sufficiently marked to warrant clinical use. Nencki and Krolikowski (**1888**) found after the administration of this compound, that dihydroxyquinoline methyl carbonic acid can be isolated from the urine, and that, therefore, a second hydroxy group is formed in the organism, as is also the case with phenol and pyrocatechol.

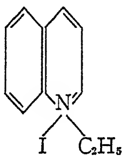
Recently Bailey and McElvain (**1930**) synthesized a series of tetrahydro- and decahydroquinoline derivatives in which alkyl benzoic acid radicles were added to the nitrogen. Some of these were found to have marked local anesthetic properties combined with a comparatively small toxicity. But since this effect is more closely related to the benzoyl group than to the quinoline radicle further discussion in this connection is unnecessary.

Another quaternary derivative of quinoline is **diquinoline-1,1-dimethyl-1,1-disulfate,**

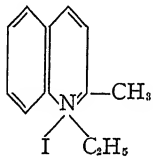


prepared by Ostermeyer (1884), which according to Hoppe-Seyler (1888) produces within five minutes peripheral motor paralysis in frogs after the subcutaneous injection of 0.01 gram. Durduffi (1889) found that it has an atropine-like action on the vagus endings antagonizing muscarine.

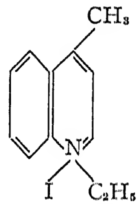
Hunt and Renshaw (1929) studied a series of methylated quaternary quinoline derivatives in regard to their effect on the blood pressure.



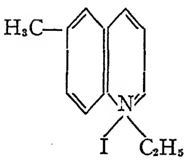
I
Quinoline ethiodide



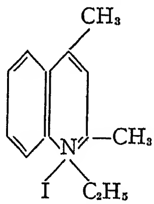
II
2-Methylquinoline ethiodide



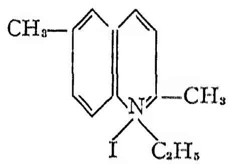
III
4-Methylquinoline ethiodide



IV
6-Methylquinoline ethiodide



V
2,4-Dimethyl quinoline ethiodide



VI
2,6-Dimethyl quinoline ethiodide

With subcutaneous administration the minimal fatal dose for mice was 0.12 mg. per gram for I, III, and VI, 0.11 mg. per gram for V, 0.10 mg. per gram for II, and 0.085 mg. per gram for IV. They found little evidence that these compounds have a direct action on the autonomic nervous system. I, II, and III caused a moderate fall of the blood pressure; IV and V had little or no effect, whereas VI frequently produced a rise of the blood

pressure, the cause of which was not determined. They found that the fall of the blood pressure cannot be prevented by premedication with atropine and that it is, therefore, of a different type than the fall of blood pressure observed after the administration of muscarine. In these experiments the introduction of methyl groups into different positions of quinoline ethiodide as in II, III, and IV has very little effect on the pressor action. This is in sharp contrast with the results found by Fredericq and Terroine to be produced by the introduction of a methyl group into the quinoline ring. As mentioned before these investigators found 2-methylquinoline, 4-methylquinoline, and 6-methylquinoline to be about four times as toxic for the heart of the tortoise as was quinoline itself.

Grabe, Nahme and Seelkopf (1932) studied the toxicity of **8-hydroxy-quinoline-metho-chloride** and of **propyl-** and **allyl-hydroxy-quinolinium-methylbenzol sulfonate.** They found that the hydroxyquinoline metho-chloride was fatal for mice in doses of 0.2 gram per kilogram, the propyl derivative in quantities of 0.5 gram per kilogram and the allyl compound in doses of 0.14 gram per kilogram. The latter causes convulsions in mice; in cats 0.02 to 0.05 gram per kilogram causes excitement followed by central depression, larger doses (0.13 gram per kilogram) are fatal, causing vomiting, respiratory stimulation and convulsions. In doses of 0.01 gram per kilogram the two alkyl substituted compounds have no effect on the nitrogen metabolism, and the effect of the unsubstituted compound seems also to be not very marked in this respect in normal dogs; starved animals respond to the administration of 0.1 gram per kilogram by a marked decrease of the protein metabolism.

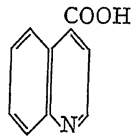
The compounds discussed in this chapter show a marked increase of the "curare" action as far as this has been studied, due to their change into quaternary bases. Furthermore it has been shown that ethylamine bound to the nitrogen atom of the quinoline ring does not yield the same sympathomimetic action as when bound to the 2- carbon of the ring. Introduction of alkyl radicles into the nitrogen of tetrahydroquinoline yields powerful antipyretics (kairoline); introduction of a hydroxy group into the benzene ring increases this effect (kairine); and masking of the hydroxy group reduces it (ethyl thalline).

Chapter VI.

Quinoline Carboxylic Acids.

Introduction of a carboxyl group frequently changes the toxicity of the new compound as compared with that of the mother substance. So, for instance, the toxic phenol is changed to the less toxic salicylic acid, the toxic santonin into the less toxic santonic acid and the butyl alcohol into the butyric acid. A similar reduction of the toxicity is obtained by introducing a carboxyl group into the quinoline ring.

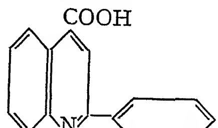
Quinoline-4-carboxylic acid,



cinchoninic acid, was first obtained by oxidation of cinchonine and can be prepared synthetically by the method of Pfitzinger (1886). It consists of fine needles crystallizing with one mol of crystal water, or of monoclinic platelets containing two mols of water of crystallization. It loses this water at 100° C., softens at 236° C., and melts at 253° to 254° C. It is slightly soluble in water and in alcohol and insoluble in ether, and it forms water-soluble salts. This compound, according to Rotter (1917), is only slightly toxic for frogs, the fatal dose being 0.05 gram. A one per cent solution inhibits the activity of the isolated frog heart, but this effect is reversible by washing with Ringer's solution. The compound does not affect the uric acid excretion.

Cinchophen.

Introduction of a phenyl group in the 2- position yields **2-phenylquinoline-4-carboxylic acid, atophan or cinchophen,**



This compound was first synthesized by Doebner and Gieseke (1887), and later by another method by Pfitzinger (1888). At present it is prepared by numerous other methods which are recorded by E. Waser in "Synthese der organischen Arzneimittel," Stuttgart, 1928. Cinchophen consists of small colorless needles melting at 212° to 213° C., or a white yellowish powder. It has a bitter taste and is insoluble in water, soluble in 20 parts of boiling alcohol, 25 parts of boiling acetone and 250 parts of boiling benzene. It is soluble when heated with acids. When mixed with 15 per cent sodium hydroxide it dissolves temporarily, and then solidifies in the form of a thick paste of very fine needles of the sodium salt. A saturated solution of cinchophen yields with platinic chloride a precipitate of yellow-brown crystals. According to the United States Pharmacopeia cinchophen gives, in addition, the following characteristic tests: One gram of the drug dissolved in an excess of ammonia, is heated on the water bath until all ammonia is evaporated, the residue is dissolved in 20 cc. of water and filtered. With silver nitrate the filtrate yields a white, with lead acetate a yellowish, and with copper sulfate a green precipitate. Further tests which also serve for the differentiation of cinchophen and neocinchophen are given by Eckert (1930). Kofler and Dernbach (1932) succeeded in isolating two forms of crystals from cinchophen by microsublimation under reduced pressure which differ as to their "crystal-optic" constants and as to their melting points. The stable form melts at 211° to 213° C. and consists of rectangular crystalline tablets of the rhombic system. The metastable compound has a melting point of 196° to 197° C. and forms massive crystals of the triclinic system.

Rotter (1917) found cinchophen five times more toxic than unsubstituted quinoline-4-carboxylic acid; in 34 gram frogs doses of 0.01 gram produce a general depression, followed by paralysis after a period of increased reflex excitability. Ullmann (1923), working with leucotropine, a mixture of cinchophen and methenamine, also noted depression, and with intravenous injections, miosis, which can be antagonized by atropine; but Starkenstein (1924) stated that the miosis also occurs in atropinized eyes.

Rotter (1917) stated that the *heart* survives after the beginning of the paralytic stage and is later arrested in systole. The intravenous injection of 35 mg. of the sodium salt into rabbits produces a slowing of the pulse rate and an increase of the amplitude,

but these phenomena are only of short duration and normal activity is restored very soon, as previously observed by Starkenstein (1913). Ullmann (1923) found a slowing of the frog heart with diastolic tendency and final arrest in diastole. He believed that the circulatory effects are due to peripheral vagus stimulation because he and Starkenstein found the same effect after vagotomy. He also found that guinea pig intestine shows an increase of pendular movements and of tone, which can be antagonized by atropine. Starkenstein (1924) observed, however, that rabbit and guinea pig small intestines are inhibited by cinchophen and concluded that the intestinal stimulation observed *in situ* cannot be due to peripheral vagus stimulation. Stake (1929) found that cinchophen reinforces the effect of epinephrine on the uterus.

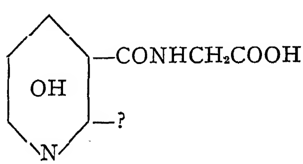
Cinchophen has *antipyretic* properties. Starkenstein (1920) observed that subcutaneous and intravenous administration of 0.5 to 1.0 gram produced a reduction of temperature in normal rabbits, but the oral administration of 1.0 gram had no effect. Because it is effective in heat-puncture fever he assumed that the antipyretic action is due to depression of the central heat-regulating mechanism. Ullmann (1923) was, however, inclined to explain the antipyretic action on the basis of vagus stimulation, as indicated by the work of Dresel (1922), Gottlieb (1890), and Isenschmid (1913).

The *antiphlogistic* action of cinchophen has been emphasized by Klemperer (1913), Starkenstein, Salus and Wiechowski (1913), Heller (1913) and others. Starkenstein found that with subcutaneous and intravenous, but not with local administration, cinchophen prevents the mustard oil chemosis of the rabbit eye. This failure of the local administration indicates that some systemic action is involved in this reaction; since the effect persists after the removal of the superior cervical ganglion, it cannot be a sympathetic action as assumed by Abl (1913). Similar results were obtained by Dohrn (1913). But Fuerst (1925), who studied this phase of the cinchophen action more closely, found that the anti-inflammatory action is of a different type than that produced by acids and calcium salts, the action of which is explained by a decrease of the carbon dioxide binding power of the serum and a consequent increase of the ionization of calcium ions. She further found that the analgetic action goes parallel with the fall of temperature and occurs only with toxic

doses. This was confirmed by Schikorr (1932) and by Hesse (1930), who found it to be ineffective in even slightly toxic doses. Laqueur and Magnus (1921) also observed no beneficial effect with therapeutic doses in pulmonary edema produced by phosgene, nor did Hanzlik and Tainter (1923) in edema produced by paraphenylenediamine. Ikeda (1916) found that cinchophen develops anti-inflammatory reactions in the frog mesentery and in this respect is synergistic with quinine. In this connection the observation of Hermann (1931) is of interest. He determined the total calcium of rabbit's blood and the calcium bound to proteins and found that the intravenous injection of 0.3 gram per kilogram of cinchophen caused a decrease of the calcium bound to proteins. But Schikorr (1932) found no indication that the antiphlogistic action of cinchophen is due to mobilization of calcium.

Schittenhelm and Ullmann (1913), and Mendel (1922) reported more or less marked *leucopenia* in patients after the use of cinchophen; Roesler and Jarczyk (1912), on the other hand, saw no effect in this direction in myeloid leucemia. Ullmann (1923), who studied a large series of patients in this respect found that leucopenia was not a regular phenomenon after the administration of cinchophen.

As to the *fate* of cinchophen in the organism it was already pointed out by Nicolaier and Dohrn (1908) that after the administration of cinchophen the urine assumes a reddish color which turns green on addition of hydrochloric acid. Four years later Dohrn isolated from the urine two compounds, 2-phenyl-8-hydroxy-4-quinolinecarboxylic acid and hydroxy pyridinuric acid.



The former was also isolated by Skorczewski and Sohn (1912). They found after the administration of cinchophen, besides the increased excretion of uric acid, which will be discussed below, the appearance of a positive diazo reaction, the greenish color reaction observed by Dohrn, a yellow precipitate after the addition of phosphotungstic acid and a dark green color after the

addition of a mixture of ammonium sulfate and ammonia. These reactions were said to be caused by 2-phenyl-8-hydroxy-4-quinolinecarboxylic acid, an opinion which was also expressed by Dohrn. Stransky (1931) found that in rabbits cinchophen is also excreted with the bile.

The diazo reaction, however, may also be an expression of a toxic action on the tissue in case urochromogen is also present. This question was studied by Greinert (1914), who came to the conclusion that the diazo reaction after administration of cinchophen is very similar to the clinical diazo reaction, but that the presence of urochromogen can be excluded with certainty, and that urochrome (Weiss) is also not increased in cinchophen urines. The increased quantity of the excreted neutral sulfur, also discovered by Skorczewski and Sohn (1912), indicates, however, the excretion of a compound of the proteinic acid fraction. This may be due to the effect on the uric acid metabolism. It may also be due to an improved excretion of certain proteinic acids under the influence of cinchophen, so that a primary decomposition of cells needs not to be assumed. Although Greinert does not consider these phenomena symptoms of a toxic action, they should be kept in mind in view of the toxic reactions which will be discussed below.

The main effect of cinchophen consists in the increase of the *uric acid excretion* as already observed by Nicolaier and Dohrn (1912). This increase may be very considerable, and may last as long as the administration of the drug is continued. After the discontinuation it is followed by a decrease of excretion. The excretion of uric acid depends also on the diet, inasmuch as with purine-free diet, the excretion returns to the normal level, even when administration of the drug is continued. With purine diet, however, the decrease may be postponed for several days. During the period of maximal uric acid excretion, the uric acid level of the blood is reduced to a minimum, but returns to normal after discontinuation of the drug.

As to the mechanism of this action three theories have been advanced: Starkenstein (1912) gave the first explanation for the increased elimination of uric acid after the administration of cinchophen. He assumed that under the influence of cinchophen the nucleoproteins are more rapidly decomposed, thus producing an increase of the endogenous uric acid. This assumption was apparently supported by the findings of Skorczewski and Sohn (1912), .

who found an increase of neutral sulfur, indicating increased metabolic activity, and by the experiments of Rosenberg (**1913**), who found that by perfusing the liver of dogs with a cinchophen solution the purine depots in the liver are mobilized. Similar conclusions were also reached by Retzlaff (**1913**), although he considered especially the possibility of a mobilization of the existing uric acid under the influence of the first doses of cinchophen. Griesbach and Samson (**1919**), Lennox (**1925**), and Grabfield and Pratt (**1931**) also tried to explain the cinchophen action, at least in part, by mobilization of uric acid depots. Later Starkenstein (**1920**) himself agreed that many phenomena point toward an improvement of the uric acid excretion through the kidney, and that the extent of this elimination depends on the amount of uric acid stored in the organism. This assumption seems to be supported by the experiments of Schroeder (**1932**), who found that the administration of cinchophen and neocinchophen prevents the storage of uric acid in the kidney of the rat as observed in normal animals after the intravenous injection of 100 mg. of uric acid per kilogram body weight. The excretion of uric acid into the intestine as observed by Schroeder and Raginsky under these conditions is, however, not affected by cinchophen. After the administration of cinchophen Denis (**1915**) found no change of the creatine content of the blood, and this indicates that a metabolic action of cinchophen is not very probable.

The second theory was advocated by Mendel (**1922**), who believed that the leucopenia, observed after the administration of cinchophen, is due to a destruction of white blood cells which would account for the increased uric acid elimination. But it has already been mentioned that leucopenia is not a constant phenomenon after the administration of cinchophen, and this theory, thoroughly discussed by Ullmann (**1923**), has been entirely discarded.

The third theory on the cinchophen action was advanced by Weintraud (**1911**). He pointed out that during the period of increased uric acid excretion the output of total nitrogen and total sulfur is not changed, which is difficult to reconcile with an increased protein metabolism. The fact that the uric acid output is most marked on the first day of administration of cinchophen, that it decreases thence even when the drug is continued in larger doses, together with the sudden decrease after the discontinuation of the drug, indicates that presumably only the available deposits

of uric acid are excreted, because of an increased permeability of the kidney. This is in accordance with the recent findings of Bergami (1930) that with the simultaneous intravenous administration of uric acid and cinchophen the uric acid content of the organs is smaller than those of the animals which received only uric acid, whereas the amount of uric acid found in the kidney seems to be slightly increased, or at least not diminished. Weintraud's theory was supported later by Frommherz (1911), Frank and Bauch (1911), Frank and Przedborski (1912) and by Bass (1914). They observed that the influence of cinchophen on the elimination of uric acid by the kidney is also indicated by the reduction of the uric acid level in the blood during the period of increased output with the urine, as found by McLester (1913), Folin and Lyman (1913), Haskins (1913), Fine and Chace (1914), and Frank and Pietrulla (1914).

Soon after discontinuation of the drug and of the increase of uric acid excretion, the decrease of the uric acid level in the blood is followed by a rise; these wave-like changes may be explained by a refilling of the uric acid depots, or by an exhaustion of the secretory mechanism, previously stimulated by cinchophen. That the function of the kidney is stimulated by cinchophen is also indicated by the results reported by V. C. Myers and Killian (1921), who found that under the influence of cinchophen the excretion of chlorides and of urea is also enhanced, especially when the level in the blood is higher than normal. Opinions vary as to the mechanism of this effect on the elimination. Stern (1925) is inclined to assume that a loose dissociable compound between uric acid and the drug is formed, perhaps by means of hydrotropism, observed by Neuberg (1916). The existence of such compounds has been demonstrated by the observations of Gibbs (1929) that the uric acid in bird's blood and urine circulates in the form of an unknown, water soluble compound, which can be precipitated by acetone. That the permeability of the membranes of the secretory apparatus is not changed, is suggested by the reports of Faludi (1928), who found that cinchophen in physiologic concentrations does not change the velocity of ultrafiltration of serum and plasma through membranes. On the other hand, Frank (1930) found in diffusion experiments of dyes into gels, that cinchophen favors the diffusion.

Zulzer (1911) thought that the increase of uric acid excretion by cinchophen in gout was so typical, that it would allow a differ-

entiation between gout and other joint affections. Recently Lublin (1930) made a comparative study on the effect of cinchophen and salicylic acid on the excretion of uric acid in gout. He found that salicylic acid is superior to cinchophen in the ability to increase the concentration of uric acid in the urine and the total uric acid excretion, but nevertheless, cinchophen was found to be superior clinically inasmuch as after salicylic acid no symptomatic improvement could be noticed. Grabfield and Pratt (1931) confirm the occasional failure of cinchophen to increase the uric acid excretion in gout. This seems to support the view of Klemperer (1913) that the clinical efficiency of cinchophen does not depend so much on its effect on the excretion of uric acid as on its antiphlogistic properties. Hesse (1930) found that cinchophen has very little or no analgetic effect in normal animals, but that it appears to be more effective in inflamed tissues.

It has been stated that the *toxicity* of cinchophen is very low; Hanzlik, Scott, Weidenthal, and Fettermann (1921) stated that although the side actions of even large doses are less marked than those seen with salicylic acid, cinchophen may cause epigastric pain, presumably due to local irritation, circulatory depression and kidney injury, as was already pointed out by Loening (1913). Cinchophen has been used extensively, clinically, and in uncontrollable doses by the laity in the form of proprietary and patent medicines. The toxicity of cinchophen appears to vary with different animals. With parenteral administration Risi (1932) found as minimal fatal dose for guinea pigs 0.90 gram per kilogram, for rabbits 0.95 gram per kilogram, and for dogs 0.62 gram per kilogram. Barbour and Lozinsky (1923) gave the minimal fatal dose for dogs after oral administration as 1.25 gram per kilogram and von Fuerth and Kuh (1930) as 1.0 gram per kilogram for rabbits. Rabinowitz (1930) gave an extensive review on this subject, and the following tables indicate that cinchophen cannot be considered a harmless drug, because severe toxic symptoms and even fatal accidents have been reported.

Table 3 gives 49 fatal accidents after the administration of cinchophen or cinchophen derivatives; all these patients developed jaundice sooner or later after the administration of the drug and died within a comparatively short time after the first manifestations of liver damage had developed, indicating the violent pathological reactions produced in the liver. It is important to note that fatal accidents may occur within a short time even with

TABLE 3.—*Fatalities after Cinchophen and Related Drugs.*

No.	Author	Sex and Age	Drug and Dose. Period of Administration	Clinical Symptoms	Time of Death after Onset of Symptoms and Autopsy Findings
1	Cabot (1925)	Male 42	Weldona 3 packages	Gastro-intestinal disturbances, jaundice	Yellow atrophy of the liver
2	Langdon Brown (1926)	Female 69	Cinchophen 120 grams 10 weeks	Gastro-intestinal disturbances, jaundice	Died after 8 days
3	Langdon Brown (1926)	Female 36	Atoquinol 130 grams 5 months	Gastro-intestinal disturbances, jaundice	Died after 10 days
4	Wilcox (1926)	Male 69	Cinchophen 6 grams 1 week	Gastro-intestinal disturbances, jaundice	Died after 28 days
5	Wells (1926)	Female 63	Cinchophen 200 grams 4½ months	Gastro-intestinal disturbances, jaundice, coma	Died after 10 days
6	Hitzenberger (1927)	Female 21	Jodatophan 5 grams i.v.	Toxic hepatitis	Died after 10 days
7	Singer (1927)	Female 56	Jodatophan 5 grams i.v.	....	....
8	Rake (1927)	Male 54	Cinchophen Large quantity	Jaundice	Cirrhosis of the liver
9	Weil (1928)	Male 47	Cinchophen Therap. doses for 8 weeks	Jaundice	Yellow atrophy of the liver

TABLE 3.—*Fatalities after Cinchophen and Related Drugs.*—(Continued)

10	Loewenthal (1928)	Female 55	Cinchophen Large doses 6 months	Jaundice	Died after 7 days
11	Loewenthal (1928)	Female 55	Cinchophen Therap. doses 8 weeks	Jaundice	Died after 5 weeks
12	London Letter (1928)	Female 55	Cinchophen 3 times daily 3 weeks	Jaundice	Yellow atrophy of the liver
13	London Letter (1928)	....	No data given		
14	Sutton (1928)	Female 27	Cinchophen 75 tablets	Jaundice	Died after 2½ months
15	McVicar and Weir (1929)	Female 37	Cinchophen	Jaundice	Acute yellow atrophy of the liver
16	Reichle (1929)	Female 20	Cinchophen and oxyliodide Large doses	Jaundice	Acute yellow atrophy of the liver
17	Reichle (1929)	Female 46	Cinchophen Large doses 3 years	Jaundice	Acute yellow atrophy of the liver
18	Anderson and Teter (1929)	Female 48	Oxyliodide 600 tablets 7 months	Jaundice	Died after 9 days, acute yellow atrophy of the liver
19–20	Tannhauser (1927)	Two fatalities; no details			

TABLE 3.—*Fatalities after Cinchophen and Related Drugs.*—(Continued)

No.	Author	Sex and Age	Drug and Dose. Period of Administration	Clinical Symptoms	Time of Death after Onset of Symptoms and Autopsy Findings
21	Stacy and Vazant ..... (1930)	Female 52	Cinchophen 1-3 tablets daily 6 weeks	Jaundice	Died after 16 days
22	Rabinowitz .... (1930)	Male 45	Cinchophen Therap. doses Long time	Jaundice	Died after 6 days, nodular hyperplasia portal cirrhosis
23	Rabinowitz .... (1930)	Female 51	Cinchophen Therap. doses 4 weeks	Jaundice	Died after 8 days, subacute yellow atrophy of the liver
24	Rabinowitz .... (1930)	Male 26	Cinchophen 4.5 grams	Jaundice	Died after 10 days
25	Rabinowitz .... (1930)	Female 39	Cinchophen Large doses 6 months	Jaundice	Yellow atrophy of the liver
26	Walker .... (1931)	Male 43	Cinchophen 6 grams	Jaundice	Died after 12 days, yellow atrophy of the liver
27	Walker .... (1931)	Female	Cinchophen Ca. 47.5 grams 1½ years	Jaundice	Died after 14 days
28	Parson and Harding.... (1931)	Female 63	Cinchophen Unknown quantity	Jaundice	Died after 4 days, yellow atrophy of the liver
29	Parson and Harding.... (1931)	Female 67	Cinchophen Unknown quantity	Jaundice	Yellow atrophy of the liver

TABLE 3.—*Fatalities after Cinchophen and Related Drugs.*—(Continued)

30	Parson and Harding.... (1931)	Female 40	Cinchophen Large quantity 6 months	Jaundice	Died after 1 week, yellow atrophy of the liver
31	Parson and Harding.... (1931)	Female 46	Cinchophen Unknown quantity	Jaundice	Died after 4 days, yellow atrophy of the liver
32	Morris .... (1931)	Male 60	Cinchophen Ca. 86 grams 2½ months	Jaundice	Died after 1 week, yellow atrophy of the liver
33	Ross .... (1931)	Female 42	Neocinchophen	Jaundice	Yellow atrophy of the liver
34	Ross .... (1931)	Female 58	Quinophen 9 grams	Jaundice	Yellow atrophy of the liver
35	Ross .... (1931)	Male 41	Neocinchophen Cinchophen	Jaundice	Liver small and yellow
36	Berger and Schweid.... (1931)	Female 63	Cinchophen 324 grams 4 months	Jaundice	Died after 3 months, septic peritonitis, toxic cirrhosis of the liver
37	Berger and Schweid.... (1931)	Male	Cinchophen 85 grams 3 weeks	Jaundice	Died rapidly, acute yellow atrophy of the liver
38	Beaver and Robertson.. (1931)	Male 37	Cinchophen 25 tablets 5 weeks	Gastric symptoms, jaundice	Died after 12 days, yellow atrophy of the liver
39	Beaver and Robertson.. (1931)	Female 57	Oxyliodide Unknown quantity Several periods	Gastric symptoms, jaundice	Died after 29 days, yellow atrophy of the liver
40	Beaver and Robertson.. (1931)	Male 62	Oxyliodide	Early toxic symptoms, jaundice, second week	Died after 5 months, yellow atrophy of the liver

TABLE 3.—*Fatalities after Cinchophen and Related Drugs.*—(Continued)

No.	Author	Sex and Age	Drug and Dose. Period of Administration	Clinical Symptoms	Time of Death after Onset of Symptoms and Autopsy Findings
41	Bogen (1931)	Female 19	Cinchophen 55 grams 5 weeks	Gastro-intestinal disturbances, jaundice	Died after 3 weeks, toxic necrosis and atrophy of the liver
42	Elliot (1931)	Female 24	Oxyliodide + Cinchophen 84 grams 4 weeks	Gastro-intestinal disturbances, jaundice	Died after 12 days
43	Hoegler (1931)	Male 59	Ascanol Dose ?	Gastro-intestinal disturbances, jaundice	Died after several weeks, yellow atrophy of the liver
44	Lind (1932)	Female 39	Cinchophen 5.85 grams	Gastro-intestinal disturbances, jaundice	Yellow atrophy of the liver
45	Winfield (1932)	Female 49	Cinchophen 30 tablets 16 days	Gastro-intestinal disturbances, jaundice	Died 25 days after first symptoms
46	Cabot, Chapman, Mallory (1931)	Female 71	Farastan Dose ?	Gastro-intestinal disturbances, edema, jaundice	Died within 1 week, yellow atrophy of the liver
47	Weis (1932)	Male 26	Cinchophen 4 grams daily 3 months	Jaundice	Yellow atrophy of the liver
48	Weis (1932)	Male 65	Cinchophen 8 tablets daily 4 months	Jaundice	Yellow atrophy of the liver
49	Weis (1932)	Female 64	Farastan 4 tablets daily 4 months	Jaundice	Yellow atrophy of the liver

clinical doses and it seems possible, therefore, that hypersusceptibility may play an important part in this phenomenon. On the other hand, experiments of Risi (1932) seem to indicate that cinchophen has neither accumulative nor habit-forming qualities, and the rate of accidents is rather low, being about 1:500,000 (Davis, 1932).

In Table 4, 58 severe intoxications are collected; all showed more or less marked symptoms of liver damage, but recovered. In these cases it is also interesting to note that the daily administration of even as little as three grams per day for two days, may produce very marked intoxication.

TABLE 4.—*Severe Intoxications after the Administration of Cinchophen and Related Drugs, but with Recovery.*

No.	Author	Sex and Age	Drug, Dose and Time of Administration	Clinical Symptoms	Recovery
1	Worster Drought (1923)	Male 59	Cinchophen 18 grams	Gastro-intestinal disturbances, jaundice	Several weeks
2	Klinkert .... (1926)	Female	Atophanyl 15 doses 5 cc.: Cinchophen 83 grams	Gastro-intestinal disturbances, jaundice	Several weeks
3	Klinkert .... (1926)	Female 55	Atophan 70 grams	Gastro-intestinal disturbances, jaundice, urobilinuria	4 weeks
4	Klinkert .... (1927)	Male 60	Atophan 80 grams 2½ months	Ascites	Recovery
5 6 7	Evans .... (1926)	....	Cinchophen (1) 10 tablets (2) 1 gram (3) ?	Jaundice	Slow recovery
8	Glover .... (1926)	....	Atophanyl 10 injections	Jaundice	Slow recovery
9 10	Wilcox .... (1926)	....	Cinchophen	Jaundice	Slow recovery
11	Kingren .... (1927)	Female 31	Diiodatophan 5 grams i.v.	Jaundice	4 weeks
12	Hitzenberger ... (1927)	Male 60	Diiodatophan	Toxic symptoms	Recovery
13	Schwartz .... (1927)	....	Diiodatophan	Toxic symptoms	Recovery

TABLE 4.—*Severe Intoxications after the Administration of Cinchophen and Related Drugs, but with Recovery.*—(Continued)

No.	Author	Sex and Age	Drug, Dose and Time of Administration	Clinical Symptoms	Recovery
14	Haudeck .... (1927)	Male 32	Diiodatophan	Toxic symptoms	Recovery
15 16 17	De Redenze .... (1927)	Female 52 Female ?? Female 52	Cinchophen 18 grams Several grams 48 tablets	Jaundice, toxic symptoms	6 weeks 7 weeks 7 weeks
18 19	Rabinowitz ..... (1928)	Male 33 Male 39	Cinchophen 15 grams 5 months 13 grams 10 days	Jaundice	3 months 4 weeks
20	Klinkert .... (1928)	Female 65	Atophan 60 grams 4 weeks	Jaundice	5 weeks
21	Dassen .... (1929)	Female 29	Cinchophen	Jaundice	4 weeks
22	Motzfeld .... (1929)	Female 27	Atophan 117 grams 2 months	Jaundice	2 months
23	Braun .... (1929)	Female 45	Atophanyl 15 days i.v.	Jaundice	3 months
24	Frenzel .... (1929)	Male 55	Atophan 6 grams 2 days	Jaundice	3 weeks
25	Grolnick .... (1930)	Female 45	Weldona (Cinchophen) Small dose	Jaundice	Slow recovery
26 27	Rabinowitz ..... (1930)	Female 37 Female 31	Cinchophen 0.4 gram daily, 2 months 20 tablets	Jaundice	2 months 7 weeks
28-40	Kessel .... (Rabinowitz) (1930)	13 cases	....	....	....
41 44	Hench .... (Rabinowitz) (1930)	4 cases	....	....	....

TABLE 4.—*Severe Intoxications after the Administration of Cinchophen and Related Drugs, but with Recovery.*—(Continued)

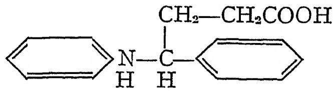
No.	Author	Sex and Age	Drug, Dose and Time of Administration	Clinical Symptoms	Recovery
45 46	Vajda .... (1930)	Female 55 Male 60	Cinchophen 60 tablets 59 tablets	Jaundice	Very slow
47 48	Ross .... (1931)	Male 26 Male 68	Neocinchophen Cinchophen	Jaundice Jaundice	Very slow Very slow
49	Sherwood ...... (1931)	Male 27	Cinchophen 4.87 grams 5 days	Jaundice	Slow
50	Eimer .... (1931)	Male 52	Cinchophen 115 grams 41 days	Skin eruptions, jaundice	Recovery after 14 weeks
51	Winfield .... (1932)	Male 45	Cinchophen Dose ?	Gastro-intestinal disturbances, jaundice	Slow recovery
52	Winfield .... (1932)	Female 31	Cinchophen 9.75 grams 2 weeks	Gastro-intestinal disturbances, jaundice	Slow recovery
53	Gargill .... (1932)	Female 47	Oxyliodide 5.6 grams 2 weeks	Loss of appetite, jaundice	Slow recovery
54	Gargill .... (1932)	Female 47	Cinchophen 36-48 tablets Oxyliodide 24 capsules	Gastro-intestinal disturbances, jaundice	Slow recovery
55	Hoegler .... (1931)	Female 52	Arcanol 2 times 2 tablets at diff. times	Jaundice after each attempt	Recovery
56	Hoegler .... (1931)	Male 21	Arcanol 16 tablets	Gastro-intestinal disturbances, jaundice	Slow recovery
57	Hoegler .... (1931)	Male 20	Arcanol Dose ?	Jaundice	Recovery
58	Schleimer ...... (1932)	Male 13	Atophanyl i.v. 5 injections, 3 weeks later 10 injections	Subicteric coloration of the skin, pain in gastric region, erythema	Slow recovery

A. von Müller (1913), Herrick (1913), Phillips (1913), Schelling (1927), Miller (1931), and Gargill (1932) noted that in addition to these severe intoxications, scarlatiniform rashes are not infrequently seen after cinchophen.

These reports indicate that cinchophen is not the harmless drug which it was generally considered, and that it may be advisable to give the drug only under medical control so that it may be discontinued with the appearance of the first adverse symptom.

Churchill and Wagoner (1931) studied the effect of large doses of cinchophen in dogs. These animals received daily, twenty-seven times the human therapeutic dose of 22 mg. per kilogram, or 595 mg. per kilogram. After from eight to ten doses they refused to eat, and died after ten, seventeen and twenty days. Autopsy revealed gastric ulcers, and some yellowish areas over the surface of the liver, showing varying degrees of liver necrosis. Another animal receiving only two of the above doses, died on the ninth day. In all animals the blood urea was first increased, later decreased, and the bromosulfophthalein test showed an increased retention of the dye. The reason for this toxicity is not yet elucidated. Reichle (1932) found that subcutaneous administration of cinchophen in single doses of 1 gram per kilogram killed rats within 24 hours. Continued parenteral administration (0.2 gram per kilogram) did not cause death, but towards the end of the treatment the animals showed symptoms which might be interpreted as an expression of hypersensitiveness. Feeding of cinchophen in doses of approximately 20 mg. a day to rats did not induce cirrhosis, even when the liver was depleted of glycogen or injured by chloroform. He believed, therefore, that the toxic effects observed in man are due either to natural hypersensitiveness or the development of an hypersensitive state. Risi (1932) gave parenterally increasing doses of cinchophen to dogs, guinea pigs and rabbits. He observed after death degenerative changes of the organs which were most marked in liver, kidney and heart. These tissue changes were characterized by microvascularization, cloudy swelling and fatty degeneration of the protoplasm with pycnosis, caryolysis and caryorrhexis of the nuclei. Myers and Goodman (1932) administered for seventeen days to dogs daily 0.03, 0.06, and 0.15 gram per kilogram with the food, rabbits received 0.3 gram per kilogram in the same way for 45 days. Histological examination of the liver revealed that cinchophen causes damage of the liver cells after comparatively short periods of time

and that the degree of the toxic action varied directly with the dose of the drug. They found that dogs are evidently more sensitive than rabbits and that the icteric index and the urobilinogen test do not indicate the extent of the liver damage as found in these animals upon histologic examination. Hatcher (1928) studied the toxicity of **γ-anilino-γ-phenylbutyric acid,**



an impurity which is frequently present in cinchophen preparations. This substance occurs as a white crystalline powder, melting at 193° C. At this temperature it liberates carbon dioxide with the formation of a base $C_{15}H_{17}N$, which, unlike cinchophen, is readily attacked by oxidizing agents. The oral administration of 250 mg. of this substance to cats produces nausea and vomiting, and 1 gram is followed by increased nervous excitability and convulsions. Daily administration of 100 mg. for four weeks did not produce toxic symptoms aside from a loss of weight. Similar negative results were obtained in dogs, so that there is no evidence that this contaminant can be credited with the toxic phenomena, especially with the yellow atrophy of the liver.

Icterus and yellow atrophy of the liver, however, have been reported after the administration of several quinoline derivatives as, for instance, with quinaldine, by Cohn (1895), with yatren, by Zieler and Birnbaum (1922), Schuebel (1924) and Michael (1922), with analgen by Maas (1895), and with plasmoquine by Cordes (1927). All these compounds have the quinoline nucleus in common, and this may therefore be responsible for the toxic action.

Furthermore, Starkenstein and his followers believed in an increased decomposition of proteins in the liver by cinchophen. They presented some evidence in support of this, especially with larger doses. The appearance of the diazo reaction after the administration of cinchophen, which is very probably of a harmless nature, may indicate pathologic changes, and the leucopenia not infrequently observed may indicate toxic effects of cinchophen, not sufficiently understood. That cinchophen is not without any effect on the liver function may be seen from Frank's report (1930) that small doses (0.1 gram) increase the excretion of dyes with the bile, whereas larger doses increase the secretion of bile but reduce the elimination of the dyestuff, which indicates a cer-

tain degree of liver damage. Taubmann (1927) studied the effect of cinchophen on the bile. First he noticed that after the administration of cinchophen the digestion of fat is distinctly reduced; then he found that the drug is excreted with the bile and that this cinchophen bile inhibits the digestion of starch and fat.

The fact that cinchophen increases the biliary flow and that it is excreted with the bile induced Pribram to suggest the use of **2-(p-iodophenyl)-6-iodoquinoline-4-carboxylic acid (Biloptin)** as a contrast agent for fluoroscopy of the gall bladder. However, it has been found to be very toxic and, as shown above, fatal accidents are not uncommon. According to Hermann (1927) it is also apt to produce kidney disturbances, for which he considers the iodophenyl group responsible. Orator and Walchshofer (1927) found after oral administration of fairly large doses to rats, that most organs, and especially the liver, showed marked fatty degeneration. Recently Lichtman (1931) suggested a test for liver function by means of cinchophen. He found that in patients suffering from liver disturbances, the excretion of cinchophen is higher (up to 42 per cent), as compared with that in normal persons (7 to 21 per cent).

After cinchophen had found such an extensive use, a great number of derivatives were put on the market, mostly under proprietary names, so that their constitution is not easily discernible. On account of the danger arising from the indiscriminate use of cinchophen, the most common of these are recorded in Table 5.

The number of patent medicines containing cinchophen and cinchophen derivatives cannot be estimated, such names as Weldona, Van Ard's, Cass, Harrel's rheumatism cures certainly do not indicate any relation to cinchophen, although it is one of the constituents of these preparations.

Of other cinchophen preparations only atochinol and neocinchophen (tolysin) are more extensively discussed in the literature.

Atochinol (atoquinol), 2-phenylquinoline-4-carboxylic acid allyl ester,

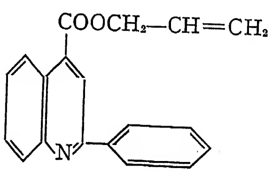


TABLE 5.—*Cinchophen and its Derivatives.*

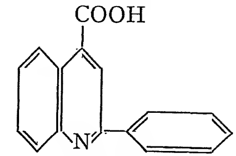
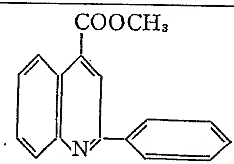
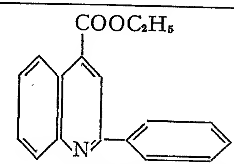
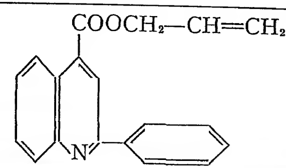
No.	Proprietary Name	Chemical Name	Chemical Formula
1	Cinchophen	2-Phenylquinoline-4-carboxylic acid	
2	Atophan K	2-Phenylquinoline-4-carboxyl-methylester	
3	Acetrine	2-Phenylquinoline-4-carboxyl-ethylester	
4	Atochinol	2-Phenylquinoline-4-carboxyl-allylester	

TABLE 5.—*Cinchophen and its Derivatives.*—(Continued)

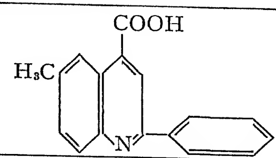
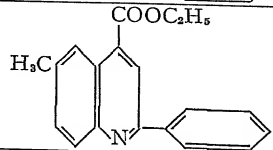
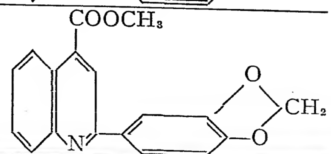
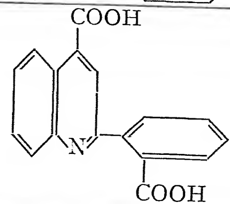
No.	Proprietary Name	Chemical Name	Chemical Formula
5	Paratophan	2-Phenyl-6-methylquinoline-4-carboxylic acid	
6	Tolysin Novatophan Neocinchophen	2-Phenyl-6-methylquinoline-4-carboxyl-ethylester	
7	Synthaline	2-Piperonylquinoline-4-carboxyl-methylester	
8	Lytophan	2-(o-Carboxyphenyl)-4-quinoline-carboxylic acid	

TABLE 5.—*Cinchophen and its Derivatives.*—(Continued)

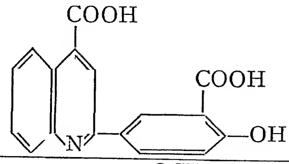
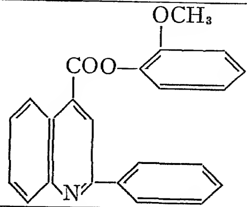
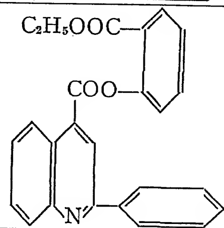
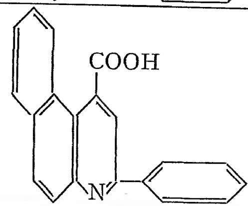
9	Hexophan	2-(p-Hydroxy-m-carboxyphenyl)-quinoline-4-carboxylic acid	
10	Guphen	2-Phenylquinoline-4-carboxyl-guaiacolester	
11	Cinchosal	Ethyl-2-phenylcinchoninyl-salicylate	
12	Diapurine	2-Phenyl-beta-naphthol-quinoline-4-carboxylic acid	

TABLE 5.—*Cinchophen and its Derivatives.*—(Continued)

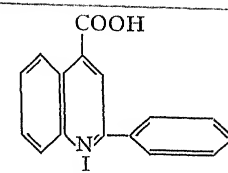
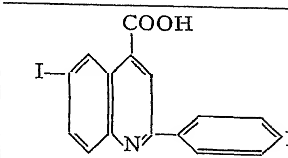
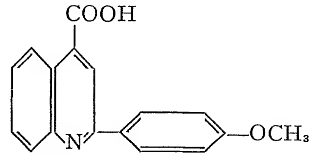
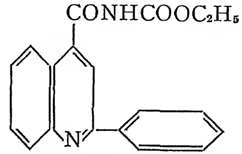
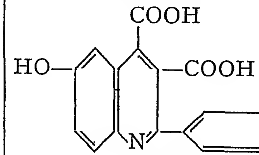
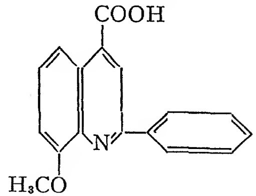
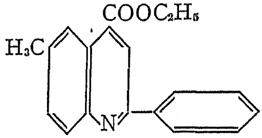
No.	Proprietary Name	Chemical Name	Chemical Formula
13	Farastan	N-Iodo-2-phenylquinoline-4-carboxylic acid	
14	Biloptin	2-(p-Iodophenyl)-6-iodoquinoline-4-carboxylic acid	
15	Oxyliodide	Hydroiodide of cinchophen	......
16	Quinophan	Brand of cinchophen	......
17	Agotan	Brand of cinchophen	......
18	Phenoquine	Brand of cinchophen	......
19	Leucotropine	2-Phenylquinoline-4-carboxylate of methenamine	......
20	Irriphan	Strontium salt of cinchophen	......
21	Atophanyl	Solution of cinchophensodium and sodium salicylate (10% with addition of 0.16% of p-aminoethanol hydrochloride)	......

TABLE 5.—*Cinchophen and its Derivatives.*—(Continued)

22	Erycon	2-(p-Methoxyphenyl)-4-quinoline-carboxylic acid	
23	Fantan	2-Phenyl-cinchoninylurethane	
24	Esophan	2-Phenyl-6-hydroxy-3,4-quinoline-dicarboxylic acid	
25	Isotophan	2-Phenyl-8-methoxy-quinoline-4-carboxylic acid	

consists of slightly yellow crystals, melting at 30° C., insoluble in water, alcohol and ether, more soluble in acids. According to Roethlisberger (1920) it has the advantage that it is tasteless, produces no side actions even with continued administration and is as effective as cinchophen in its analgetic properties. Uhlmann and Burow (1921) claimed that the uric acid excretion is more marked with atoquinol than with other preparations of this type in dogs and in man. The antipyretic properties were said to be more marked than with cinchophen.

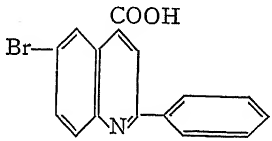
Neocinchophen, 6-methyl-2-phenylquinoline-4-carboxylic acid ethyl ester,



is a yellowish-white powder melting at 75° to 76° C., very little soluble in water or alkali, but easily soluble in organic solvents. V. C. Myers and Killian (1921) found that it increased the excretion of uric acid through the kidney in the same way as cinchophen. The choleretic properties are also present as with cinchophen (Spurling and Hartman, 1928) and it is said to be less apt to produce liver damage. From the reports of von Fuerth and Kuh (1930) it appears that it is absorbed somewhat more slowly from the intestinal tract than cinchophen, without undergoing saponification prior to its absorption.

Barbour and Lozinsky (1923) claimed that it is non-toxic for dogs in doses up to 50.0 gram per kilogram, in contrast with the minimal fatal dose of cinchophen (1.25 gram per kilogram); the safety exponent for neocinchophen would therefore be 1/150 as compared with 1/63 for cinchophen. Its lower toxicity was also confirmed by von Fuerth and Kuh (1930), who found that the minimal fatal dose for rabbits was 1.4 gram per kilogram as compared with 1.0 gram per kilogram of cinchophen. In comparing the toxic dose found by Barbour and Lozinsky in dogs with this minimal fatal dose determined for rabbits it appears that there may be a great variation in the susceptibility of different species. Neocinchophen is probably partly oxidized in the organism and appears in the urine as dioxymethylphenylquinoline carboxylic acid.

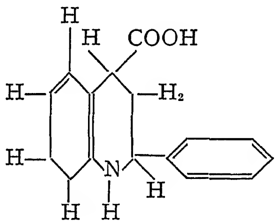
Brot (1923) studied the pharmacologic action of **6-bromo-2-phenyl-4-quinoline carboxylic acid.**



This compound is two and one-half times more toxic for cold-blooded animals than is cinchophen. In opposition to cinchophen it produces in warm-blooded animals a primary central stimulation, increased reflex excitability, and later depression. In cold-blooded animals it causes, like cinchophen, central motor depression, which on the subsequent days is followed by hyperexcitability. It stimulates and later depresses the respiration. It stimulates the vagus peripherally and perhaps also centrally, causing slowing of the heart. It reduces the body temperature like cinchophen, but on the whole it is less effective on the uric acid excretion.

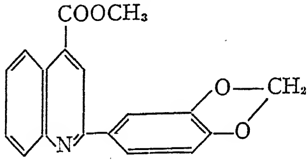
It was shown above that hydrogenation increases the toxicity of many compounds as, for instance, quinoline and tetrahydroquinoline, and the same holds true for cinchophen.

Tetrahydroatophan,



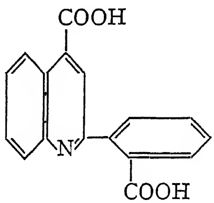
prepared by Skita and Brunner (**1916**) consists of pale yellow crystals with a melting point of 165° to 167° C., soluble in water. Pohl (**1918**) found it to be much more toxic than cinchophen with regard to the nervous symptoms, 0.015 gram per 36 grams frog producing tetanus and muscular twitchings which may last over a long period. On the other hand, the toxic action on the heart seems to be reduced almost to zero. Similar results were obtained in mammalian experiments. Severin (**1918**) used it with some benefit in doses of 0.1 gram which were gradually increased to 1.0 to 1.2 grams in the treatment of motor and sensory paralysis of spinal and peripheral origin.

Synthaline, methyl-2-piperonyl-cinchoninate,



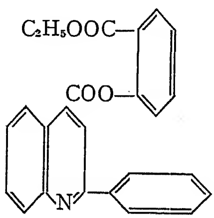
consists of a greenish-yellow crystalline powder which melts at 135° C., is insoluble in water and alkali, difficultly soluble in alcohol, soluble in ether and benzene, and easily soluble in methyl alcohol. Klemperer (1913) found that it did not enhance the uric acid excretion but that it was nevertheless beneficial in the treatment of gout, mainly by its analgetic properties. This he found true also with **2-phenylsulfonate-7-methylquinoline-4-carboxylic ethyl ester.**

Lytophan, 2-(o-carboxyphenyl)-4-quinoline carboxylic acid,



was studied by Gudzent and Keip (1921), who found it less toxic than cinchophen for different animals, the effect on the uric acid excretion being about the same with both drugs.

Cinchosal, ethyl-2-phenylcinchoninyl salicylate,



was studied by Boenheim (1914) as to its effect on the excretion of uric acid in dogs. He found that the administration of 2.08 grams three times daily reduced the excretion of uric acid 25 per cent and increased that of allantoin 13.4 per cent.

The relation of chemical constitution to the effect on the uric acid excretion, the uricosuric action, of cinchophen was first

studied by Niccolaier and Dohrn (**1908**). They found that quinoline 4-mono- and 2,4-dicarboxylic acid had no effect. The introduction of one or two methyl groups did not improve the action, but the introduction of a phenyl group in the 2- position produced a marked stimulation of the excretion. A hydroxy or methoxy radicle in the 6- position seems to antagonize this effect, but the hydroxy group in the 3- position seems to be less harmful. The same holds true for the introduction of hydroxy groups in the phenyl ring, while the introduction of two phenyl radicles in the 2- and the 3- position seems to enhance the uric acid excretion, but not more so than a single phenyl in the 2- position. From these experiments it appears that the phenyl group in the 2- position of the quinoline ring is essential for the effect on the elimination of uric acid.

The same conclusion was reached by Impens (**1912**), who investigated in this respect a great number of quinoline carboxylic acids in man. He summarizes his results and also those of Niccolaier and Dohrn in Table 6.

Impens also found that the introduction of a phenyl group in the 2- position is indispensable and that alkyl groups in the same position are ineffective. Since 2-phenylquinoline does not increase the uric acid output the additional introduction of a carboxyl group preferably in position 4- is essential. Doubling either the phenyl or carboxyl group neither decreases nor increases the uricosuric action. Introduction of a hydroxy group in the para position of the phenyl ring does not suppress the action, but the introduction of methyl, methoxy, or of two hydroxy groups does so. While introduction of a hydroxy group in the 3- position of the quinoline ring does not prevent the action, its introduction in position 6-, or that of a methoxy compound, prevents it, and in position 8- it weakens the action. Introduction of an amino group in position 6- reduces the action; replacement of one of the amino hydrogens by a benzoyl group abolishes it. This was confirmed by Ciusa and Luzatto (**1913**). The introduction of an alkyl group differs in its effect with the position. In position 6- it does not interfere, but weakens the effect in position 3- and abolishes it in position 7-. Esterification of the carboxyl group with an ethyl or acetyl group does not affect the efficiency, as is the case with the heavy alcohols such as cyclohexanol, glycol and others. The closure of the carboxyl group by an amido group does not remove the specific action, but this is abolished by re-

TABLE 6.—*Uricosuric Action of Cinchophen Derivatives.*

Effective	Ineffective
2-Phenylquinoline-4-carboxylic acid	2-Phenylquinoline
2-Phenylquinoline-4-carboxylic acid ethyl ester	Di-hydroxyquinoline
2-Phenylquinoline-4-carboxyl-amide	Quinoline-4-carboxylic acid
2,3-Diphenylquinoline-4-carboxylic acid	Quinoline-2,4-dicarboxylic acid
2-Phenyl-6-methylquinoline-4-carboxylic acid	2-Methylquinoline-4-carboxylic acid
2-Hydroxyphenylquinoline-4-carboxylic acid	2-Methylquinoline-3-carboxylic acid
2-Phenyl-3-hydroxyquinoline-4-carboxylic acid	2-Methylquinoline-3,4-dicarboxylic acid
2-Phenylquinoline-4-carboxylic acid acetol ester	2,3-Dimethylquinoline-4-carboxylic acid
Less Effective	2,3-Dimethylquinoline-3,4-dicarboxylic acid
2-Phenyl-6-aminoquinoline-4-carboxylic acid	2-Phenyl-6-hydroxyquinoline-4,8-dicarboxylic acid
2-Phenylquinoline-4,8-dicarboxylic acid	2-Phenyl-6-methoxyquinoline-4-carboxylic acid
2-Phenylquinoline-3,4-dicarboxylic acid	2-(Dihydroxyphenyl)-quinoline-4-carboxylic acid
2-(O-hydroxyphenyl)-7-methylquinoline-4-carboxylic acid	2-Phenyl-6-benzoylaminoquinoline-4-carboxylic acid
2-Phenyl-8-methoxyquinoline-4-carboxylic acid	2-Phenyl-7-methylquinoline-4-carboxylic acid
Anhydride of 2-phenylquinoline-4-carboxylic acid	2-Phenyl-8-carboxylic acid ethylester-quinoline-4-carboxylic acid
2-Phenyl-3-ethylquinoline-4-carboxylic acid	2-(P-methoxyphenyl)-3-phenylquinoline-4-carboxylic acid
2-Phenylquinoline-4-carboxylic acid phenyl ester	2-(P-tolyl)-quinoline-4-carboxylic acid
2-Phenylquinoline-4-carboxyl-cyclohexanol ester	2-(P-methoxyphenyl)-quinoline-4-carboxylic acid
	2,3-Diphenylquinoline-4-carboxyl-amide
	2-Phenylquinoline-4-carboxylic acid urea
	2-Phenylquinoline-4-carboxylic acid-salicylic acid ester
	2-Phenylquinoline-4-carboxylic acid ester of ethyleneglycol mono-salicylate
	2-Phenylquinoline-4-carboxylic acid ethanol amide

placement of the hydrogen atoms of the amido group by ethoxy radicles.

Impens states that no relation could be established between the chemical properties of these compounds and their efficiency as to the elimination of uric acid, and that his results were obtained empirically. Since the mechanism of the action of cinchophen has not yet been elucidated, it is difficult to state a priori which physical properties are of importance. A comparative study of the physicochemical properties (surface tension, permeability, partition coefficient) of effective and ineffective compounds as,

for instance, quinoline 4-carboxylic acid and 2-phenylquinoline-4-carboxylic acid may show relations leading towards a better understanding of the physiologic properties of the drug.

Kaku (1928), who studied a series of nine cinchophen derivatives (as shown in Table 7) in rabbits, in relation to the excretion of uric acid, reached different conclusions.

TABLE 7.—*Cinchophen Derivatives Studied by T. Kaku.*

(1) 2-(P-methoxyphenyl)-8-methylquinoline-4-carboxylic acid
(2) 2-Phenyl-8-methylquinoline-4-carboxylic acid
(3) 2-(P-methoxyphenyl)-7-methylquinoline-4-carboxylic acid
(4) 2-(P-methoxyphenyl)-quinoline-4-carboxylic acid
(5) 2-(P-methoxyphenyl)-6-methylquinoline-4-carboxylic acid
(6) 2-Phenylquinoline-4-carboxylic acid
(7) 2-Phenyl-7-methylquinoline-4-carboxylic acid
(8) 2-(P-methoxyphenyl)-6,8-dimethylquinoline-4-carboxylic acid
(9) 2-Phenyl-6,8-dimethylquinoline-4-carboxylic acid

Kaku found that the methoxy group in para position in the phenyl radicle increases the uricosuric action considerably as compared with that of cinchophen. After the subcutaneous administration of 0.2 gram per kilogram rabbit Matao (1931) also observed a considerable increase in the uric acid excretion in the bile, and compared, in this respect, the effect of the drug in normal, splanchnectomized and vagotomized animals.

Kaku further stated that substitution of methyl groups in positions 6- and 7- had no effect on the efficiency of either the methoxy or the unsubstituted 2-phenylquinoline-4-carboxylic acid, while in position 8- it increases the action above that of any of the other preparations studied. This statement is also in contradiction to Impens's results, who found that introduction of a methyl group in position 6- does not affect the uricosuric action but abolishes it in position 7-. Kaku finally claimed that introduction of two methyl groups in position 6- and 8- reduces the efficiency of the compounds. According to his results 8-methyl-2-p-methoxyphenyl quinoline-4-carboxylic acid is more effective than 2-phenylquinoline-4-carboxylic acid.

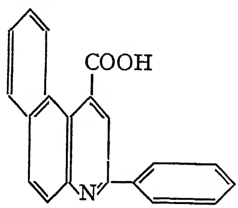
This discrepancy between the results of Kaku and Impens may be explained by the fact that the former performed his experiments in rabbits and the latter in men. From the studies of Wiechowski on uric acid metabolism it is known that in rabbits and dogs the uric acid is usually largely oxidized to allantoin. Since Starkenstein (1911) found that in rabbits and dogs an increase in the excretion of uric acid parallels a decrease of allantoin, it is evident that this increased uric acid excretion is

due to a disturbance of the oxidative processes, presumably in the liver. It may be considered as established, however, that in man the metabolic processes are not affected by cinchophen. Furthermore Kaku found in his rabbits that the uric acid level in the blood was increased after the administration of the drugs, which increase was most marked with cinchophen after from two to six hours, followed by a slow decrease. With 2-(p-methoxyphenyl)-quinoline-4-carboxylic acid it generally reached its maximum after twelve hours, followed by a marked increase of uric acid excretion above the normal. This observation is also in contradiction to the clinical experience on the uric acid level in the blood after the administration of cinchophen, and it may be considered a well established fact that in man the uric acid level is always markedly decreased following the administration of the drug. These differences seem to indicate that the effect of phenylquinoline carboxylic acids in man on the one hand, and in rabbits and dogs on the other, follows two different mechanisms, and this would explain the reason for numerous controversies on this subject. It illustrates the risk of transferring uncritically the results obtained in animal experimentation to the conditions in man.

Piung Hun Ri (1931) studied the uric acid level in the blood of dogs and rabbits in different sections of the body after subcutaneous administration of 2-(p-methoxyphenyl)-quinoline-4-carboxylic acid. He believed that splanchnicectomy interferes with the mobilization of uric acid by this compound and that vagotomy has no effect in this respect.

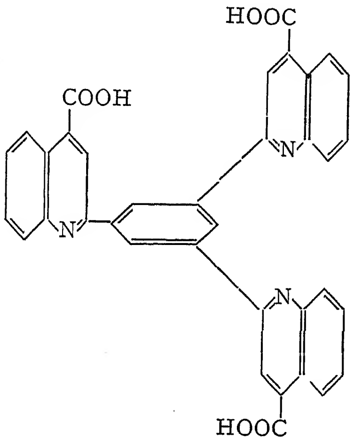
In a second paper Kaku (1929) again confirmed the well-known findings of others that phenylquinoline and substituted phenylquinolines have no uricosuric action, that hydrogenation as in tetrahydrocinchophen and decahydrocinchophen reduces the action as had already been reported by Luzatto and Ciusa (1913) (quoted from Fraenkel).

Diapurine, 2-phenyl-5,6-benzoquinoline-4-carboxylic acid,



prepared by Ciusa and Luzatto (1913) has also marked uricosuric properties.

Tri-atophan,



a compound synthesized by von Braun has no effect on the uric acid excretion (Lublin, 1930).

The *relation between toxicity and chemical structure* of the cinchophen derivatives in regard to the effect on the central nervous system and on the isolated frog heart has been studied by Rotter (1917). The former is characterized by a progressive depression followed by a period of increased reflex excitability, finally passing into complete paralysis; the cardiac action consists in loss of tone with diastolic tendency.

The comparison of the data concerning the toxicity reported in Table 8 with the uricosuric action of the corresponding compounds studied by Impens shows that the introduction of a phenyl group in 2- position of the quinoline ring is essential for the specific action and also increases the toxicity; that the introduction of a methyl group in position 3- or 7- and that of an amino or hydroxy group in position 6- decreases both. The same holds true for the substitution of a methyl group in the para position of the phenyl ring. It is interesting and rather peculiar that methyl and ethyl radicles have such a different effect on the toxicity, the former producing a reduction and the latter a marked increase. It is also surprising that masking of the hydroxy group in position 6- by a methyl radicle increases the toxicity, while it abolishes the uricosuric action completely, especially in view of the fact

TABLE 8.—*Relation between Chemical Constitution and Toxicity of Cinchophen Derivatives.*

(L. Rotter.)

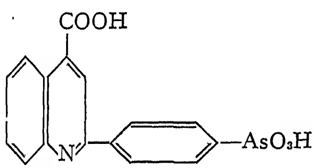
Compound	Fatal Dose in Grams per 35 Grams Frog	Fatal Concentration for the Isolated Frog Heart	Degree of Toxicity and Remarks
Quinoline-4-carboxylic acid ...	0.05	1:1000	0
2-Phenylquinoline-4-carboxylic acid ...	0.01	0.5:1000	+
2-(P-ethylphenyl)-quinoline-4-carboxylic acid ...	0.0075	0.1:1000	++ (vagus stimulation)
2-Phenyl-3-ethylquinoline-4-carboxylic acid ...	0.03	5:1000	±
2,3-Diphenylquinoline-4-carboxylic acid ...	0.03	3:1000	±
2-Phenyl-7-methylquinoline-4-carboxylic acid ...	....	....	± (more toxic)
2-Phenyl-6-methylquinoline-4-carboxylic acid ...	....	0.5:1000	± (besides depression)
2-(P-tolyl)-quinoline-4-carboxylic acid ...	....	0.5:1000	± (muscular twitchings)
2-(P-chlorophenyl)-quinoline-4-carboxylic acid ...	0.0075	0.5:1000	++
2-(O-hydroxyphenyl)-quinoline-4-carboxylic acid ...	0.005	0.5:1000	++
2-(M-hydroxyphenyl)-quinoline-4-carboxylic acid ...	0.005	0.5:1000	++
2-(P-hydroxyphenyl)-quinoline-4-carboxylic acid ...	....	....	♀ nearly ineffective
2-Phenyl-6-hydroxyquinoline-4-carboxylic acid ...	....	....	♀ nearly ineffective
2-Phenyl-6-methoxyquinoline-4-carboxylic acid ...	0.005	0.5:1000	++
2-Phenyl-6-aminoquinoline-4-carboxylic acid ...	....	....	♀ practically non-toxic
Disodium salt of 2-(hydroxyphenylcarboxylic acid)-quinoline-4-carboxylic acid ...	....	....	♀ practically non-toxic
Benzoyl-aminophenol ...	....	....	♀ practically non-toxic
2-Phenyl-4,5,6-pyridinetricarboxylic acid ...	....	....	♀ practically non-toxic

that the antipyretic action of 6-hydroxyquinoline disappears entirely after methylization as mentioned above. On the other hand, introduction of two phenyl groups in position 2- and 3- of the

quinoline ring seems to decrease the toxicity and not to affect the elimination of uric acid. The same holds true for the introduction of a hydroxy group in the para position of the phenyl ring which may indicate that these preparations are superior to cinchophen in regard to their therapeutic value.

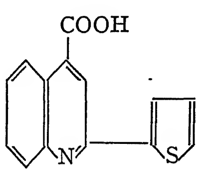
The *chologogue action* of cinchophen and some of its derivatives was studied by Brugsch and Horsters (1924). They found that **2-(p-hydroxyphenyl)-quinoline-4-carboxylic acid** is about as effective as cinchophen, 2-piperonyl-quinoline-4-carboxylic acid and 6-methyl-2-phenyl-quinoline carboxylic acid range next, that 2-(p-hydroxy-m-carboxyl-phenyl)-quinoline-4-carboxylic acid has only little and 2-(sulfophenyl)-quinoline-4-carboxylic acid and 2-(m,p-dimethylphenyl)-quinoline-4-carboxylic acid have no effect on the excretion of bile. Chabrol and Maximin (1929) confirmed the findings of Brugsch and Horsters as to the chologogue action of cinchophen.

Ogden and Adams (1925) synthesized arseno derivatives of cinchophen. They prepared **2-arsenophenylquinoline-4-carboxylic acid: 2-arsenophenyl-6-methylquinoline-4-carboxylic acid,**



their sodium salts and a series of esters, but all these compounds proved to be more toxic than arsphenamine and less trypanocidal.

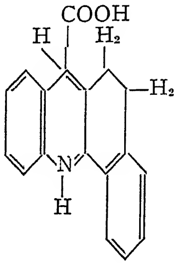
Hartmann and Wybert (1919) tried to replace the phenyl group in the cinchophen molecule by the thiophene radicle hoping to increase in this way the antiphlogistic and analgetic properties of cinchophen. This compound, **2-thienylquinoline-4-carboxylic acid,**



is prepared by condensation of acetothienone with isatin, it forms yellow platelets, melting at 211° C., which are slightly soluble in water, more so in alcohol, and very soluble in alkalies. They

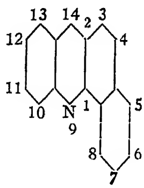
stated that according to Uhlmann and Roman this compound had marked antiphlogistic and analgetic properties. However, feeding of the drug or intravenous administration stains the animals purple within a short time and the urine assumes the color of a concentrated solution of potassium permanganate. The dyestuff could be isolated from the urine, but its chemical structure seems to be unknown.

Tetrophan, 3,4-dihydro-1,2-naphthacridine-14-carboxylic acid,*



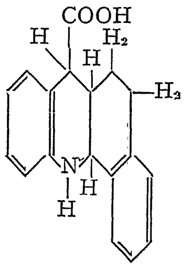
prepared by condensation of isatin with tetralon by von Braun and Wolff (1922) represents light yellow needles melting at 252° C. with the formation of carbon dioxide. Although this compound is an acridine derivative, it resembles cinchophen so closely in chemical structure that it may be discussed in this connection. This compound, however, has no uricosuric action, but stimulates the spinal cord in a way similar to strychnine. For this reason it has been used clinically in the treatment of certain nervous diseases. Mann (1922) saw good results in multiple sclerosis; his work was partly confirmed by von Hagen (1925), but Wollny (1924) found it less encouraging in this disease; he saw, however, better results in the treatment of myasthenia. In spastic spinal paralysis and in infantile spinal paralysis Elsner (1924) and von Hagen (1925) saw satisfactory results, especially in the stage of repair. Since the course of this disease is rather irregular and the number of treated and untreated cases

* With these compounds the numbering of the atoms of the ring system is as follows:



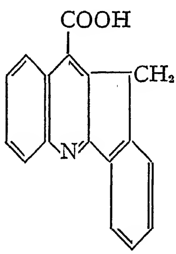
in this study is limited, further confirmation seems necessary. The initial dose, according to Elsner (**1924**), is 0.125 gram, which should be gradually increased to three times this dose three times daily. Toxic symptoms, such as spasm and positive Babinski reflex, may develop with large doses, but these disappear with discontinuation of the drug.

The **tetrahydro-tetrophan, 1,2-naphthacridine-1,2,3,4,9,14-hexahydro-14-carboxylic acid,**



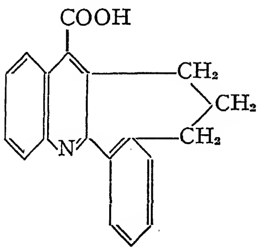
prepared by von Braun and Wolff (**1922**) is said to act in the same way as tetrophan. It appears, therefore, that the group CH_2-CH_2 is not essential for this effect.

The lower homolog,



prepared by von Braun and Stuckenschmidt (**1923**) is ineffective. These authors believe, therefore, that the characteristic action of tetrophan is based on its acridine structure.

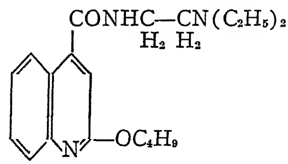
However, the higher homolog, *homotetrophan,*



prepared by condensation of isatin with benzosuberon in alkaline solution is as effective as tetrophan, so that it appears that something besides the acridine structure is essential for the pharmacologic action.

NUPERCAINE.

It has been shown that some of the quinoline carboxylic acid derivatives have analgetic properties. This prompted the synthesis of **n(β-diethylaminoethyl)-2-oxybutylcinchonamide,**



marketed under the name of **Percaine or Nupercaine.** It consists of a 2- substituted quinolinecarboxylic acid which is linked to a diethyl diaminoethylene group. This resembles very closely other alkyl substituted groups used in the synthesis of local anesthetics. Nupercaine is a colorless powder which melts at 97° C., is without taste and odor, and is easily soluble in water. The aqueous solution may be sterilized. Alkali, also soft glass, must be avoided because they precipitate the free base. The pH of the solutions should therefore range from 6.2 to 6.5, which can be accomplished by the addition of dilute hydrochloric acid.

The *local anesthetic properties* of the compound have been reviewed by Jones (1930) and by Keyes and McLellan (1931). The *pharmacologic properties* of the drug were first studied by Lipschitz and Laubender (1929). On the rabbit cornea they found that nupercaine is one hundred times more effective than cocaine which agrees with the results reported by Israel and MacDonald (1931) and Laubender and Ost (1932), who state that it is 1.5 to 2 times more effective than pantocaine. Uhlmann (1929) stated that in this respect a nupercaine solution of 1:10,000 corresponds in its efficiency to a cocaine solution of 1:100. In determinations of the local anesthetic action with the Tuerck experiment (frog foot) nupercaine in concentrations of 1:1000 was effective after one second, cocaine in the same concentration only after thirty seconds (Uhlmann, 1929). Wachtel (1929) and Rosenstein (1929) emphasize also the rapid onset and the long duration of the anesthesia. The effect on

motor nerve fibers, according to Lipschitz and Laubender (1929), is three times more marked than that of cocaine. Israel and MacDonald (1931) found it about seven times more potent than cocaine, and according to Uhlmann it is even ten times more marked and the effect can be increased by the addition of epinephrine. Israel and MacDonald (1931) found that 0.5 mg. used for spinal block anesthesia in cats caused anesthesia of four times longer duration than 20 mg. of procaine given in the same way. Hirsch (1929) stated that phenol seems to have a synergistic action with nupercaine, so that a one per cent solution of nupercaine containing 0.5 per cent phenol equals a two per cent solution of nupercaine. Hilarowitz and Bielinski (1931) found that potassium sulfate and probably magnesium salts also have a similar effect.

The effect on the circulation. Lipschitz and Laubender (1929) observed that intravenous injections of half the minimal fatal dose (1.75 mg. per kilogram) into rabbits cause fall of blood pressure, vagus pulse and cardiac irregularities. According to Uhlmann (1929) this does not occur with small doses of 0.05 mg. per kilogram; and medium doses of 0.5 mg. per kilogram cause only a distinct but short effect. In the isolated frog heart Uhlmann found that concentrations of 1:2,000,000 cause slowing and reduction of the amplitude, and concentrations of 1:1,000,000 arrest in diastole; this effect may be reversed by lavage with Ringer's solution. In man Keyes and McLellan (1931) observed in spinal anesthesia with nupercaine, a fall of blood pressure, which, however, is said to be less than that observed after procaine under similar conditions.

With the Trendelenburg frog perfusion method Lipschitz and Laubender found a slight vasoconstriction; in the rabbit ear concentrations of 1:1,000,000 have no vasomotor effect, concentrations of 1:50,000 cause vasodilatation, and more concentrated solutions of from 1:10,000 to 1:1000 give vasoconstriction, followed by dilatation which is readily antagonized by epinephrine (Uhlmann, 1929). In man Hirsch (1929) noticed hyperemia of the mucous membranes after local administration of nupercaine which could easily be antagonized by epinephrine. Schlesinger (1931) observed that the intravenous injection of from two to five cc. of a 0.6 to 1.0 per cent solution causes constriction of the pulmonary vessels, the first injection being more effective than those subsequent.

According to Uhlmann (1929) solutions of nupercaine of 0.5 : 1000 have distinct hemolytic properties on a suspension of red blood cells in saline which, however, are less marked in the presence of defibrinated blood. This was confirmed by Takatsuki (1932), who found also that concentrations, stronger than those used clinically, increase the clotting time of the blood and decrease its content of thrombin and fibrinogen.

The effect on the central nervous system. In cats and in dogs from 10 to 15 mg. per kilogram cause clonic and tonic convulsions; in rabbits the tonic type is predominant. In dogs Bond and Bloom (1931), after nasal administration of from 5 to 10 mg. per Kg., observed tremors, excitement, spasticity of the limbs, emesis, presumably of central origin, and convulsions. Fuehner (1932) found that in mice 0.1 mg. per gram seldom cause convulsions but fatal paralysis within one hour; smaller doses of 0.05 to 0.1 mg. per gram increase first the excitability and later cause epileptiform convulsions, whereas 0.01 to 0.03 mg. per gram only cause increased excitability. In frogs 0.08 to 0.09 mg. per gram cause rapid paralysis, 0.06 to 0.07 mg. per gram induce first excitement, then strychnine-like convulsions, followed by paralysis and inhibition of the reflexes.

Lipschitz and Laubender (1929) stated that the *elimination* of nupercaine is slow and the *detoxification* is very small and incomplete, which would permit a sharper dosage than with cocaine, for instance. Wahl and Knoefel (1932) found that it is very slowly absorbed when injected subcutaneously. Bond and Bloom reached the opposite conclusion, however, namely, that it is rapidly detoxified and excreted. The long duration of the local anesthetic effect is difficult to reconcile with such qualities.

Lipschitz and Laubender (1929) stated that nupercaine seemed to be only slowly absorbed from the mucous membranes. From the findings of Bond and Bloom it appears that this varies with different types of mucous membranes. They found that it is readily absorbed from the nasal, buccal and pharyngeal mucous membranes, slowly and irregularly from the mucosa of the stomach and only very slowly from the bladder and vagina. Timm (1932) reported one fatality after the urethral injection of 10 cc. of a 1.5 per cent instead of 1.5 per mil solution. Although the patient died from 30 to 40 minutes after the injection, 1.2 mg. of the base could be isolated from liver, spleen and kidney, indicating a fairly rapid absorption.

The *toxicity* of nupercaine for different animals with different methods of administration has been determined as follows:

Animal	Minimum Fatal Dose Subcutaneously Mg. per Kg.	Minimum Fatal Dose Intravenously Mg. per Kg.	Author
Frog	60	...	Lipschitz and Laubender, Fuehner
Guinea Pig	19.5	...	Bond and Bloom
Guinea Pig	...	3–4	Uhlmann
Rabbit	5–10	3–4	Lipschitz and Laubender
Rabbit	10–20	3–4.5	Uhlmann
Dog	20	...	Lipschitz and Laubender
Dog	21	...	Bond and Bloom
Mouse	70	...	Fuehner

Uhlmann pointed out that the toxicity of nupercaine with intravenous injection varies with the concentration used and the speed of the injection, also with the different veins. Using a concentration of 1 : 100 he found the minimal fatal dose for rabbits to be 10 mg. per kilogram, with more dilute solutions, 1 : 5000, it required 30 mg. per kilogram. Bond and Bloom used a 1 per cent solution for their experiments and for this reason presumably their values are slightly higher than those given above. Laubender and Ost (**1932**) found that with rapid intravenous injection nupercaine is about twice as toxic as pantocaine. MacDonald and Israels (**1932**) determined the relative efficiency of nupercaine as compared with that of cocaine as 25, cocaine being 1. Wahl and Knoefei (**1932**) assume that nupercaine is more toxic for the central nervous system than for the heart.

From these data it appears that nupercaine is more toxic than cocaine. Eichhoff (**1929**) stated that the toxicity is 5 to 9 times that of cocaine and 40 times that of procaine. This marked toxicity of nupercaine gave rise to numerous undesirable accidents shortly after its introduction, which, however, appear to have become more rare as the technic of its use was improved. From recent publications it seems to have gained a firm place as a local anesthetic (Keyes and McLellan, **1931**). But in order to illustrate the dangers derived from incorrect administration, some of the toxicologic literature will be reviewed.

Freund (**1929**) reported one fatal accident after infiltration anesthesia with 130 cc. of a 0.1 per cent solution of nupercaine. The patient collapsed ten minutes after the injection, developed clonic convulsions, cyanosis, severe cardiac disturbances and died after 45 minutes from respiratory paralysis. Since 4 mg. per kilogram was considered to be the maximal tolerated dose and this is more

than used in this instance, it may appear that this dose is too high. Siebner (1929) pointed out, however, that this dose is frequently surpassed without untoward effects. For this reason hypersensitivity for the drug must be considered as a possible cause of the toxic effect, if this is the case, great care must be exercised to avoid such accidents. Klestadt (1929) reported three cases of fatal nupercaine poisoning after surface anesthesia of the nose with 2 per cent solutions of nupercaine with the addition of epinephrine. All these patients collapsed, showed marked pallor, restlessness, fear and nausea and died from respiratory failure. Keyes and McLellan (1931) reported eight other fatalities from the literature and two of their own practice. Kuehnel (1931) reported one fatality after the perineural injection of 110 cc. of a 1 per mil solution; the main symptoms were convulsions, cyanosis and respiratory disturbances. Wirth (1931) reported a violent intoxication after injection of 35 mg. of nupercaine in preparation for removal of an exophthalmic goiter. He believed that the toxic symptoms had been due to an accidental intravenous injection of at most 10 mg. of nupercaine, which may indicate the danger of the use of nupercaine in regions with abundant vascularization. Fuehner (1931) reported two cases of nupercaine poisoning and gave a review of the literature on this subject.

Eichhoff (1929) cautioned against the use of nupercaine in lumbar anesthesia; Ziegner (1929) saw collapse after the intraspinal administration of 1 mg. and considers 0.5 to 0.8 mg. sufficient and safe. Wiedenhorn (1930) cautions also against its use in spinal, paravertebral and sacral anesthesia.

Uhlmann (1929) reported that subcutaneous injections of nupercaine solutions into rabbits caused no irritation, but according to Eichhoff (1929) such injections may produce necrosis of the margins of the wound; the same opinion was expressed by Stohr and Brandesky (1930).

The following concentrations and doses have been suggested for the different forms of anesthesia. Freund (1929) recommended 2 cc. of a 0.5 per cent, 10 cc. of a 0.1 per cent, or 20 cc. of a 0.5 per mil solution. Goldhahn (1930) used considerably higher doses, namely 400 cc. of a 0.05 per cent, 150 cc. of a 0.1 per cent and 50 cc. of a 0.2 per cent solution.

Klestadt (1929) believed 1.5 per cent to be sufficient for laryngologic operations. For the suppression of labor pain by injections into the parametrium of both sides, Gremme (1930)

suggested a solution of 0.05 per cent with the addition of epinephrine and a few drops of hydrochloric acid.

The Council on Pharmacy and Chemistry of the American Medical Association (**1931**) gives the following doses and concentrations:

Type of Anesthesia	Concentration	Maximum Dose Injected
Infiltration	1:2000 or 1:1000 0.1 cc. epinephrine per 100 cc.	100 cc.
Spinal	1:200	7.5-10 mg. (1.5-2 cc.)
Sacral	1:1000 1:500	25-35 cc. 12.5-17.5 cc.

From the publication of Deyton, Wilson and Zaus (**1932**) it appears that for infiltration anesthesia the injection of from 3 to 5 cc. of a solution of 1:5000 is not dangerous but appears to be not superior to procaine.

Chapter VII.

Aminoquinolines.

Aminoquinolines other than amino derivatives of compounds discussed so far have not been studied pharmacologically and it is only recently that N. Bramachari and his co-workers (**1931**, **1932**) published a study on the antiseptic action of 6- and 8-aminoquinoline and of some of their derivatives.

From Table 9 it appears that 6-aminoquinoline is slightly more toxic for paramecia than the 8- compound and, therefore, it differs in this respect from methyl- and hydroxyquinolines where the 8- compounds are at least more toxic for mammals. Introduction of a glycine radicle into the amino group does not improve the antiseptic action. Introduction of a hydroxy group in position 6- of the quinoline ring increases the antiseptic action of 8-aminoquinoline and 8-glycineaminoquinoline considerably but also these compounds were later found to be ineffective in malaria; masking of the hydroxy group by methylation abolishes this effect completely. This is in accordance with numerous other experiments in this line. In this series especially the compounds XI to XV are of interest because they show a similar structure as the following aminoquinoline derivative, plasmoquine, which requires a more detailed discussion.

Plasmoquine.

The experience that the antimalarial properties of methylene blue can be distinctly improved by the introduction of aminoalkyl groups induced Schulemann, Schoenhoefer and Wingler (**1932**) to synthesize several quinoline derivatives of this type. The most effective was found to be **6-methoxy-8-(α-methyl-δ-diethyl-aminobutyl)aminoquinoline, Plasmoquine,**

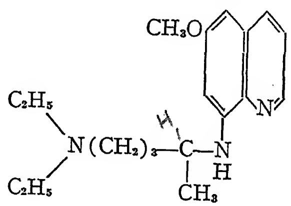


Table 9.—*Antiseptic Action of 6- and 8- Aminoquinoline and Some of Its Derivatives.*

(Measured by Their Toxicity for Paramecia.)
(U. Bramachari and co-workers.)

No.	Compound	Concentration	Effect
1	6-Aminoquinoline	1:2000	No death
		1:4000	No death
2	6-Glycineaminoquinoline	1:2000	Death
		1:4000	No death
3	8-Aminoquinoline	1:2000	No death
		1:4000	No death
4	8-Glycineaminoquinoline	1:2000	No death
5	6-Hydroxy-8-aminoquinoline	1:2000	Death in 6 min.
		1:10 000	Death in 7 min.
		1:20 000	Death in 7 min.
		1:40 000	Death in 8 min.
		1:80 000	Death in 14 min.
		1:160 000	Death in 17 min.
		1:320 000	No death in 1 hour
6	6-Hydroxy-8-glycineaminoquinoline	1:2 000	Death in 7 min.
		1:10 000	Death in 7 min.
		1:20 000	Death in 10 min.
		1:40 000	Death in 11 min.
		1:80 000	Death in 15 min.
		1:160 000	Death in 19 min.
		1:320 000	No death
7	6-Methoxy-8-glycineaminoquinoline	1:1000	No death
8	Quinine hydrochloride	1:10 000	Death in 7 min.
		1:20 000	Death in 10 min.
		1:40 000	Death in 19 min.
		1:80 000	Death in 35 min.
		1:160 000	No death in 1 hour
9	8-Aminoquinoline-p-arsanilate	1:2000	A few dead in 1 hour
		1:10 000	No death in 1 hour
10	6-Aminoquinoline-p-arsanilate	1:2000	No death in 1 hour
		1:10 000	No death in 1 hour
11	8-Aminoethylaminoquinoline hydrochloride	1:2000	Death in 3 min.
		1:10 000	Death in 35 min.
		1:20 000	No death in 1 hour
12	8-Aminoisopropylaminoquinoline hydrochloride	1:2000	Death in 20 min.
		1:10 000	Death in 35 min.
		1:20 000	90% death in 1 hour
		1:40 000	No death in 1 hour
13	6-Methoxy-8-aminoisopropylaminoquinoline dihydrochloride.	1:2000	A few dead in 1 hour
		1:10 000	No death in 1 hour
14	6-Chloro-8-aminoisopropylaminoquinoline dihydrochloride.	1:2000	Death in 1 min.
		1:10 000	Death in 4 min.
		1:20 000	Death in 12 min.
		1:40 000	Death in 30 min.
		1:80 000	No death in 1 hour
		1:100 000	No death in 1 hour
15	6-Chloro-2-methyl-8-aminoisopropylamino quinoline dihydrochloride	1:2000	Death in 30 min.
		1:10 000	No death in 1 hour
16	Aminoacetyl derivative of 8-aminoethylaminoquinoline	1:2000	90% death in 1 hour
		1:10 000	No death in 1 hour

which has some specific antimalarial action, in contrast to all compounds so far discussed which have either very uncertain and limited or no value in the treatment of malaria, for which they were originally planned. It has one definite advantage over quinine in that it has no bitter taste. Although Feiler (1928) found that plasmoquine is distinctly less toxic for paramecia than quinine when exposed to light and more toxic when kept in the dark, it seems to be more valuable in the treatment of malaria than any of the drugs so far synthesized. Roehl (1926) studied its *antimalarial* action in birds and found that it does not mobilize the defense mechanism of the host, but that it has a definite effect on the development of the plasmodia. He found that the prophylactic administration delays the appearance of plasmodia in the blood. If the administration was started on the day of the inoculation and continued for six subsequent days, 1 cc. per 20 grams body weight of a 1:50,000 solution by stomach tube was found to prevent the infection, while in the case of quinine the minimal effective concentration is 1:800, so that plasmoquine appears to be sixty times as effective as quinine in avian malaria. In the following year Godoy and Lacorte (1927) reported that the drug has specific gameticidal properties for halteridium in pigeons but did not affect the schizogenic forms. Hegner and Manwell (1927) demonstrated also the therapeutic value of the drug in avian malaria but found that it did not destroy all parasites in the blood. The specific gameticidal action of plasmoquine was also emphasized by Barber and Komp (1927), who found by the mosquito bite method that in patients who originally had 26 gametocytes per 1000 leucocytes the ratio was 8:1000 after two days of daily administration of 0.06 gram plasmoquine and 0.75 gram quinine. Those patients who still showed gametocytes in their peripheral circulation were found to be also not infectious for mosquitoes. The gameticidal action has also been emphasized by MacPhail (1927), who observed that the gametes disappeared on the fifth day with the daily administration of 0.06 gram of plasmoquine, while with the quinine alone in doses of 2 to 2.5 grams daily, they were still present after twenty days. He likewise found that the schizontes were not affected to the same extent and Whitaker (1929) also stated that they are less susceptible. As this form is readily killed by quinine it seems reasonable to combine both drugs, a method which is now generally practiced. Since the gametes are not directly involved in

the process of the disease of a malaria patient but are only the carriers of the infection to the mosquito, plasmoquine cannot be considered a therapeutic agent but rather an aid in sanitation and prevention, a fact also pointed out by Pillsbury (1930).

The *pharmacology of plasmoquine* was first studied by Eichholtz (1927), who found in cats and rabbits that 1 to 2 mg. per kilogram produce a slight fall of blood pressure with rapid recovery; larger doses of 2 to 3 mg. cause some slowing of the heart and irregularities of the cardiac action, mainly due to ventricular disfunction which may be antagonized by epinephrine. He also observed some stimulation of the central nervous system, especially in animals under light anesthesia. One of the most frequent side actions of plasmoquine, which were promptly noticed in its therapeutic application, was more or less marked cyanosis. Fischer and Weise (1927) believed that this is due to methemoglobin formation. Since this effect was greater when the blood cells were brought into contact with the solution of the drug, they assumed that it was due to an adsorption phenomenon and that the degree of the methemoglobin formation depends on the ratio of concentration of plasmoquine to the number of red blood cells. They, therefore, suggested and confirmed by experiment that smaller doses of plasmoquine might produce no, or only very slight, methemoglobinemia, an opinion which evidently was not shared by LeHeux and de Lind van Wyngaarden (1927). The latter published a more detailed study of the toxicity of plasmoquine.

TABLE 10.—*Toxicity of Plasmoquine for Different Animals.*
(Le Heux and de Lind van Wyngaarden.)
(Plasmoquine in mg. per kg. body weight.)

Animal	By Mouth			Subcutaneously			Intravenously		
	Non-effective	Toxic	Lethal	Non-effective	Toxic	Lethal	Non-effective	Toxic	Lethal
Rabbit	150	187.5	225	10	15	20	2	3	3.5
Cat	2.5	5	7.5	2.5*	3	5-7.5	2.5	2.5	5.0
Dog	....	....	20	....	10	20	....	....	....
Mouse	....	....	....	8.5	10	12.5	....	....	....
Canary	±33	50	50	16.5	25	33-50	....	....	....

* Methemoglobin formation.

As indicated by Table 10, which is taken from a later publication of the same authors (1929), there are great differences as

to the toxicity for different species. The toxic symptoms produced by the drug show two stages. The acute stage, predominant in rabbits, is characterized by slowing of the pulse, cardiac irregularities, dyspnea and depression, followed by increased reflex excitability and occasionally by convulsions from which the animals may recover. According to Tskimanauri (1931) doses of 0.3 mg. per kilogram rabbit cause a short temporary rise of the blood pressure and stimulation of the respiration which soon is followed by a depression. He assumes that the cardiac effects are indirect, presumably due to disturbances of the oxygen supply. The second or prolonged stage, characteristic for cats and dogs, consists of a slow development of cyanosis and dyspnea due to formation of methemoglobin. They also found that the excretion is very slow, only a small percentage being excreted with the urine within the first two days. The rabbit can destroy comparatively large quantities of plasmoquine; cats and dogs, much less. As indicated by the manifestation of the two stages of the poisoning, rabbits respond less readily with methemoglobin formation than do cats and dogs, presumably because the red blood corpuscles of the rabbit are less permeable to plasmoquine than those of other species. Hemolysis could only be observed in higher concentrations of the drug (above 0.1 per cent, using blood cells of cats). As to the *antipyretic properties* of plasmoquine, Girndt (1929) found that it has only insignificant or no effect on coli fever in rabbits and that only toxic doses show some antipyretic action. Thus it appears that its antipyretic action in malaria is due to its effect on the parasites and not on the host, an assumption also expressed by Cordes (1927) and Sinton and Bird (1928).

The knowledge of the pharmacologic properties of plasmoquine furnishes the key for the explanation of the *toxic symptoms*, observed especially in the beginning of its therapeutic use. Sioli (1926), who was the first to study the antimalarial properties of the drug in patients suffering from progressive paralysis under malaria treatment, already noticed the marked cyanosis and observed collapse after plasmoquine treatment. Muehlens (1927) gave 0.02 gram five times daily or 0.05 gram three times daily and noticed cyanosis and complaints of gastric pains. He also found that plasmoquine is less effective in tropical malaria and that it generally requires the simultaneous administration of quinine to produce cure. He, therefore, suggested the use of dragées containing 0.01 gram of plasmoquine and 0.125 gram of

quinine, given six times daily. O. Fischer (1928) considers 0.01 gram as the minimal effective dose in tertiana, the average daily dose being 0.06 gram. In malaria tropica a total dose of 0.15 gram as an injection or 0.2 gram given orally, distributed over a period of from 24 to 36 hours or of several days, was said to be sufficient to make the crescent forms disappear from the peripheral circulation within five days; but in order to prevent a relapse Fischer found it necessary to administer quinine simultaneously. He also emphasized that the dose of plasmoquine should be calculated by weight, because in weak patients undesirable side actions are more marked. Schulemann and Memmi (1927) claimed that plasmoquine may destroy all forms of tertian and of quartan malaria. After the daily administration of three times 0.02 gram plasmoquine the fever was abolished on the first or second day and the parasites disappeared from the peripheral circulation on the fifth or sixth day. They gave 0.02 gram three times daily for seven consecutive days, followed by a pause of four days, then the same dose for three days and then gradually increased the number of plasmoquine-free days between each three-day treatment. They also emphasized that in malaria tropica plasmoquine must be combined with quinine since it affects only the gametocytes. They found that although doses of 0.05 gram twice daily may reduce the temperature and may cause the disappearance of the gametes and schizontes, this effect is slow and relapses too frequent, and furthermore, such doses are too close to the toxic dose. They found, however, the combination with quinine (0.01 gram plasmoquine with 0.125 gram quinine sulfate) very effective. They gave this dose twice daily for fourteen days, then with alternations of four days of treatment with pauses increasing from two to four days. Cordes (1927) stated that although plasmoquine is generally well tolerated, among 250 plasmoquine patients he saw six severe intoxications, four being fatal. Most of the latter had received 0.08 gram daily, and on the fourth day, when the blood was already free of ring forms, they suddenly showed severe prostration, somnolence, pain in the gastric region, vomiting, rise of temperature, jaundice and fall of hemoglobin.

The blood showed marked pathologic changes, namely macro- and microcytosis, polychromatophilia, basophilia, nucleated red blood cells and leucocytosis. The urine contained casts, bile pigments and urobiline. The patients died within 48 hours; one patient with similar symptoms recovered. Bunce (1930) in two

fatal cases found hypoglycemia which may be easily understood in the light of liver damage observed in such intoxications. Among 400 patients receiving 0.06 gram plasmoquine daily MacPhail (1927) observed toxic symptoms in 6 cases. Phelps (1927), after the same dose, observed toxic symptoms in 11 cases out of 19. The latter considers plasmoquine a very dangerous drug, which should be used only in hospitals under close observation; Bass (1930) came to the same conclusion. Manson-Bahr (1927) observed cyanosis in 3 out of 8 cases. Sinton and Bird (1928) also emphasized the narrow margin of safety but considered 0.06 gram daily a safe dosage. Phelps (1927) preferred 0.03 gram daily together with 1.2 grams quinine. Sonak (1930) pointed out that the side actions can be controlled to a great extent by giving the drug only after meals, i.e., not on an empty stomach. Hasselmann and Hasselmann-Kahlert (1928) claim that infants, 3 to 14 months of age, tolerate plasmoquine better than adults, which was apparently confirmed by Ronnefeldt (1931). Mannifold (1931) reviewed the clinical literature and published his own experiences with the drug. He believed that the combined plasmoquine-quinine treatment can be given to all classes of patients whatever their physique may be with only very few exceptions. He observed occasionally slight idiosyncrasy against plasmoquine, but believed that with sufficient attention minor incidents are of no avail and they are of importance in exceptional cases. He emphasized, however, that the drug should be given only under medical control. Whitmore (1929) believed that 0.3 mg. per kilogram or 0.0180 gram per average person is sufficient to destroy the crescent forms, and that no further plasmoquine should be necessary provided sufficient quinine is given. Barber, Komp, and Newman (1928-1929) observed that in one case a single daily dose of 5 milligrams had distinct prophylactic effect on crescent carriers. On the other hand, Napier, Butcher and Das Gupta (1932) reported that 10 mg. of plasmoquine three times weekly for three months caused a much higher incidence of malaria among the "protected" population, indicating the possibility of a provocative effect of such small doses. Kliegler and Reitler (1929) found that the treatment of a highly infected population with plasmoquine for 5 days may be sufficient to free the peripheral circulation of sexual and asexual forms. They found that 0.1 gram quinine together with 0.01 gram plasmoquine, twice daily, was sufficient to render the gametocytes of *Pl. falsi-*

parum non-infectious for anopheles. Ronnefeldt (**1931**) also saw no side actions after the daily administration of 0.01 gram plasmoquine and 0.125 gram quinine, given continuously for years in malaria prophylaxis. Sinton, Smith and Pottinger (**1930**) reported a series of complete cures after daily administration of 0.04 gram plasmoquine and 1.25 grams quinine and state that with intramuscular administration even 0.03 gram plasmoquine seems to be sufficient. James, Nicol and Shute (**1931**) found that plasmoquine had distinct prophylactic value against inoculation malaria; similar results were reported by Baker and Gill (**1932**).

Muehlens (**1927**) pointed out that plasmoquine is a valuable drug in hemorrhagic diathesis, in black-water fever and in quinine idiosyncrasy or resistance. This was recently confirmed by Biddau (**1930**), who, on the other hand, advised that plasmoquine should not be given to patients with liver disturbances, nephritis or cardiac lesions.

The administration of quinine to parturient women may induce premature labor and in such cases plasmoquine may be of value. Epstein (**1931**) found that in a concentration of 1:1,000,000 plasmoquine increases the tone and the amplitude of the contractions of the rat and guinea pig uterus and that in this respect it is ten times as potent as quinine. With systemic administration, however, the ratio of curative dose to oxytocic dose is decidedly in favor of plasmoquine as the safer drug, so that it may be preferred to quinine in parturient women.

Observations recently reported by Schallworth (**1929**) indicate that plasmoquine resistance may also be induced, because he observed in paralytic patients under malaria treatment that the effective dose had to be increased later in order to produce the same curative results.

From this it appears that plasmoquine cannot be considered as a substitute for quinine, but it seems to be valuable when quinine cannot be used, and as adjuvant in the administration of quinine on account of its specific toxicity for gametocytes which are more resistant to quinine than the schizonts. In small doses of 0.018 gram per day it may be a safe prophylactic against the transmission of malaria by mosquitoes.

Dimeplasmine is said to be a derivative of plasmoquine and to be less toxic; in regard to its effect on avian malaria it was said to compare favorably with plasmoquine. Green (**1929**) tested it in 11 malaria patients, starting with doses of from 10.8

to 12.3 mg. per kilogram and ending the treatment with quantities of 25.1 to 34.6 mg. per kilogram after the fifth day, without getting any effect on the parasites or on the malarial symptoms. This illustrates again that the results obtained in animal experiments can be transferred only with great caution to the usefulness as a therapeutic agent.

The first compound of this series synthesized by Schulemann, Schoenhoefer and Wingler was **8-diethylamino-ethylamino-quinoline** (D. R. P. 486,079, **1924**), which was of distinct curative value in malaria of birds but which was later found inferior to plasmoquine.

Fourneau, Trefouel, Bovet, and Benoit (**1931**) studied a series of substituted 8-aminoquinolines * as to their efficiency in infections of rice finches (*Padda orizivoris*) with *Hemoproteus orizivorae*. Table 11 gives the compounds, their minimal tolerated dose (MTD), the dose which was used in the therapeutic experiments, and the ratio, minimal tolerated dose to therapeutic dose, which may be called the therapeutic index for these experiments. The plus, plus-minus and zero signs indicate the efficiency, i.e., whether all, only a part or none of the treated birds were cured.

From these experiments it appears that the methoxy group in position 6- is not essential for the therapeutic effect, because several compounds, such as No. 728, are quite effective without this group. On the other hand, substitution of the methoxy group by the ethoxy group reduces distinctly the efficiency (Nos. 732-692; 698-713; 733-693; 730-710). This difference is absent with Nos. 734-716 and 665-664, compounds with a longer side chain in the 8-amino group. The higher homologs, propyl and butyloxy, are markedly less effective. We shall encounter later the similar decrease of the antimalarial action of hydroquinine, produced by the higher homologs of the methoxy group.

Introduction of ethylamino groups into the 8-amino group of the quinoline ring increases the therapeutic efficiency. However, it is essential that the substituted amino group is in position 8- as may be seen from a comparison of the therapeutic effect of Nos. 692 and 699; in the latter compound the position of the methoxy and amino groups is exchanged, being a 6-β-(diethylamino)-ethyl-amino-8-methoxy-quinoline.

* Schulemann (**1932**) pointed out that from these preparations the formula of No. 587 had already been published as example I and that of No. 600 as example II of D.R.P. 541,730 (1925) and No. 731 as example I of D.R.P. 486079 (1924). No. 710 had also been prepared in the I. G. Laboratories but it was discarded because it was more toxic than plasmoquine although easier to prepare.

TABLE 11.—*Chemotherapeutic Efficiency of 8-Aminoquinoline Derivatives.*

(Fourneau, Tréfouel, Bovet, Benoit.)

No.	Compounds	Maximal Tolerated Dose in Grams	Curative Dose in Grams	Thera-peutic Index
	I. Importance of the 6-methoxy group			
728	8-(γ-(Diethylamino)propylamino)-quinoline	0.0008	0.00002	+ 1/40
587	6-Methoxy-8-aminoquinoline	0.004	0.001	± 1/4
600	6-Ethoxy-8-aminoquinoline	0.0025	0.0006	0 1/4
732	6-Ethoxy-8-[β-(diethylamino)ethyl-amino]-quinoline	0.0005	0.000125	+ 1/4
698	6-Ethoxy-8-[β-diethylamino-α-(methyl-butylether)-ethylamino]-quinoline	0.0003	0.000075	0 1/4
733	6-Ethoxy-8-(β-diethylamino-β-isobutyl-ethylamino)-quinoline	0.0002	0.00005	± 1/4
730	6-Ethoxy-8-(γ-diethylamino-propyl-amino)-quinoline	0.00006	0.000015	+ 1/4
734	6-Ethoxy-8-(γ-dimethylamino-β-dimethylpropylamino)-quinoline	0.0006	0.000015	+ 1/40
665	6-Ethoxy-8-(γ-diethylamino-β-dimethylpropylamino)-quinoline	0.0006	0.00006	+ 1/40
694	6-Propyloxy-8-(γ-diethylamino-β-dimethylpropylamino)-quinoline	0.0006	0.00006	+ 1/10
723	6-Butyloxy-8-(γ-diethylamino-β-dimethylpropylamiño)-quinoline	0.001	0.0001	+ 1/10
	A. 8-(α-diethylaminoethylamino)-quinolines			
731	8-(β-(Diethylamino)-ethylamino)-quinoline	0.0016	0.0004	± 1/40
	(*a*) *Introduction of a methoxy group in position-6-*			
692	6-Methoxy-8-(β-diethylamino-ethyl-amino)-quinoline	0.0016	0.0004	+ 1/40
699	6-(β-Diethylamino-ethylamino)-8-methoxy-quinoline	0.003	0.00075	0 1/4
	(1) Substitution in the β-amino group by higher homologs			
718	6-Methoxy-8-(β-diisoamylamino-ethylamino)-quinoline	0.0008	0.0002	+ 1/4
	(2) Introduction of ether groups in the -α-carbon of 8-(β-diethylamino-ethylamino)-quinoline			
704	α-Methyl-methylether	0.001	0.00001	+ 1/10
703	α-Methyl-ethylether	0.0006	0.00006	+ 1/10
706	α-Methyl-propylether	0.0008	0.00008	+ 1/10
697	α-Methyl-butylether	0.0008	0.00008	+ 1/10
708	α-Methyl-isopropylether	0.0004	0.0001	± 1/4
705	α-Methyl-isobutylether	0.0008	0.0002	0 1/4

TABLE 11.—*Chemotherapeutic Efficiency of 8-Aminoquinoline Derivatives.*—(Continued)

No.	Compounds	Maximal Tolerated Dose in Grams	Curative Dose in Grams	Therapeutic Index
707	α-Methyl-isoamylether	0.0008	0.0002	0 ¼
	(3) Introduction of ether groups in -α- carbon of 8-(β-dimethylamino-ethylamino)-quinoline			
709	α-Methyl-ethylether	0.0001	0.000025	+ ¼
712	α-Methyl-propylether	0.0001	0.000025	± ¼
714	α-Methyl-butylether	0.0012	0.0003	+ ¼
715	α-Methyl-isopropylether	0.0012	0.0003	± ¼
713	α-Methyl-isobutylether	0.0008	0.0002	+ ¼
717	α-Methyl-isoamylether	0.0016	0.0004	± ¼
	(4) Introduction of phenyl radicles in the -α- carbon of 8-(β-dimethyl-aminoethylamino)-quinoline			
691	α-(p-methoxytolyl)-	0.0008	0.00008	+ 1/10
	(5) Introduction of aliphatic radicles in the -β- carbon of 8-(β-dimethylamino-ethylamino)-quinoline			
693	β-Isobutyl	0.0006	0.00015	+ ¼
	B. 8-(γ-aminopropylamino)-quinolines			
728	8-(γ-Diethylaminopropylamino)-quinoline	0.0008	0.00002	+ 1/40
710	6-Methoxy-8-(γ-diethylaminopropyl-amino)-quinoline	0.0006	0.000015	+ 1/40
	(1) *Substitution of hydrogen in the side chain*			
736	6-Methoxy-8-(γ-diethylamino-α-methyl-propylamino)-quinoline	0.00016	0.000016	+ 1/10
695	6-Methoxy-8-(γ-dimethylamino-α-ethylpropylamino)-quinoline	0.0008	0.00002	+ 1/40
696	6-Methoxy-8-(γ-diethylamino-α-ethylpropylamino)-quinoline	0.0008	0.00002	+ 1/40
716	6-Methoxy-8-(γ-dimethylamino-β-dimethylpropylamino)-quinoline	0.0012	0.00003	+ 1/40
664	6-Methoxy-8-(γ-diethylamino-β-dimethylpropylamino)-quinoline	0.0008	0.0002	+ 1/40
	6 Methoxy-8-(γ-diethylamino-α-methyl-butylamino)-quinoline (Plasmoquine)	0.00016	0.000004	+ 1/40

The substitution of the amino group of the side chain seems to be of no great importance, dimethyl, diethyl and diisoamyl amino derivatives of otherwise identical constitution show no material differences.

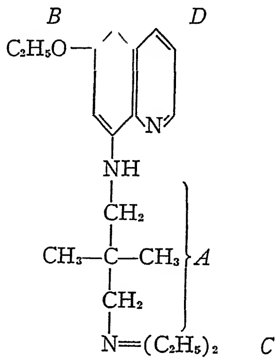
Introduction of ether groups into the carbon side chain (Nos. 704, 703, 706, 697) reduces the efficiency as compared with that of the unsubstituted compounds (No. 692). The isocompounds of this type (Nos. 708, 705, 707) are even less effective. Introduction of a phenolic ether as in No. 693 appears to be less harmful. It seems to be of no consequence whether alkyl radicles are introduced in the α or β carbon of the side chain.

Lengthening of the side chain increases the efficiency (Nos. 728-731).

From these compounds, No. 692, containing two carbons in the side chain, Nos. 728 and 710 with three carbons and Nos. 695, 716, 734 and 664 with a substituted three carbon side chain appear to be worth further study. Apparently the most effective of these compounds is No. 710 which, like plasmoquine, caused complete cure in a fraction of the treated animals with 1/150 of the minimal tolerated dose. Sergent, Catanei, Trensz and Sergent (1931) studied this preparation in canary birds infected with *Plasmodium relictum*. They found it about ten times as toxic as quinine; however, the curative dose was only one-tenth of the minimal tolerated dose. This compared favorably with quinine with which the therapeutic and the minimal tolerated dose are the same. Preparation No. 710 affects the plasmodia in the same way as quinine does. Small doses of 0.0005 gram given before and after the inoculation of the birds with *Plasmodium relictum* may prevent the infection completely.

Monier (1931) tested preparation No. 664 in paralytic patients inoculated with *Plasmodium vivax*. He found that the compound had some therapeutic value. Intramuscular administration of 0.04 gram appeared to be not sufficient, daily doses of 0.1 gram caused severe side actions (pallor, weakness, and pain in the legs). Doses of 0.06 to 0.08 gram in two fractions appeared to be well tolerated. A dose of 0.03 gram caused disappearance of the parasites from the peripheral circulation. The injection of a total dose of 0.5 gram was said to be sufficient to avoid relapses. After the third or fourth injection only schizonts could be discovered. Preparation No. 710 was tested by the same author in 2 paralytics infected with *Plasmodium vivax* and in 3 patients suffering from malaria. It was found to be very effective against *Plasmodium vivax;* a single dose of 0.04 gram was sufficient in one instant to make the parasites disappear from the peripheral circulation. Side actions were not observed.

Bovet (1932) studied these compounds as to their local anesthetic properties and the 6-ethoxy-(γ-diethylamino-β-dimethylpropyl)-aminoquinoline (No. 665),



also as to its pharmacologic action. This compound has marked local anesthetic properties. The dihydrochloride forms yellow needles which are very soluble in water. The aqueous solution is yellow and very acid, but may be decolorized by partial neutralization without precipitating the base. The aqueous solution can be sterilized at 105° C. When tested on the rabbit cornea the *local anesthetic action* equals that of nupercaine and its depressant action on the *nervus lingualis* of the dog is two times more marked than that of nupercaine.

The effect on the *circulation* is characterized by a fall of the blood pressure which, however, is easily controlled by the administration of epinephrine. In dogs, with the intravenous injection of small doses, this fall is only moderate and short, but larger doses cause a sharp fall with a slow return to the normal level. The heart is slowed but the inotropic effect occurs only with higher concentrations. The intravenous injection of 0.0005 gram per kilogram causes vasoconstriction in the kidney and spleen. Concentrations of 0.0015 to 0.0025 per cent depress the *smooth muscle* of the isolated rabbit intestine.

The *toxicity* is of the same order as that of nupercaine. With subcutaneous injection the minimal fatal dose for the mouse is 0.0025 gram per 20 grams bodyweight, for the rabbit 0.018 gram per kilogram and for the dog 0.02 gram per kilogram. The toxic symptoms are paralysis and stiffness of the limbs, especially of the

hind legs, excitation and opisthotonus. The drug disappears rapidly from the circulation.

As to the relation between chemical constitution and pharmacologic action Bovet made the following statement: Comparison of the local anesthetic action of compound No. 665 with other members of this series shows that among the isomers of No. 665 those with the most ramified side chain (A) are the most effective. Variations of the number of carbons of the straight side chain between 2 and 5 have no marked influence on the local anesthetic properties, which indicates that there is no very close relation between the molecular weight and the local anesthetic action. The latter is, however, materially increased by the introduction of alkyl groups into the side chain. The ethoxy group (B) in position 6- is generally more effective than the methoxy group, whereas introduction of such groups into the side chain does not increase the efficiency materially. As to the substitution in the amino group (C), the diethyl substitutes are generally more effective than the corresponding methyl derivatives. The quinoline ring (D) seems also to be essential for the local anesthetic action. 6-Methoxy-8-aminoquinoline has slight local anesthetic properties, whereas the corresponding phenyl compound has none. It appears, therefore, that the local anesthetic action depends upon different structural characteristics as the antimalarial properties.

Fourneau and his collaborators (**1930**) synthesized a series of cinchophen, nitro- and aminoquinoline derivatives which they tested in regard to their antimalarial action in birds. The compounds which were studied more closely are given in Table 12.

A comparison of the toxicity of these compounds reveals the following facts. In 50 per cent of the cases the nitroquinoline derivatives are not more toxic than the corresponding amino derivatives. Replacement of the amino groups by the arsonic acid group does not increase the toxicity, as the arsonic acid compound may even be less toxic; No. 587 being ten times less toxic than No. 588. The introduction of a methoxy group in No. 573 does not modify its toxicity (No. 593). The ethoxy derivative, No. 600, is ten times less toxic than the corresponding methoxy derivative, No. 587. The latter is twenty times more toxic than No. 597, although only the positions of the methoxy group and of the amino groups are exchanged. The compounds, Nos. 588, 600 and 601, have been tried in man as to their antimalarial action

TABLE 12.—*Chemical Constitution and Toxicity of Amino and Nitro Quinoline Derivatives.*

(Fourneau.)

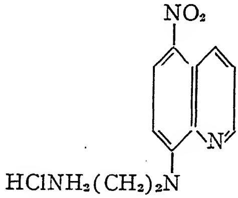
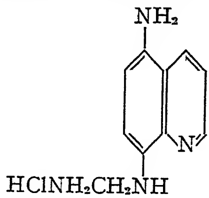
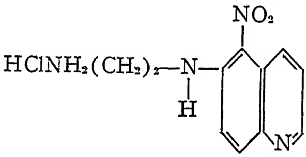
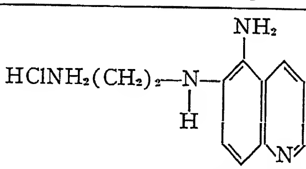
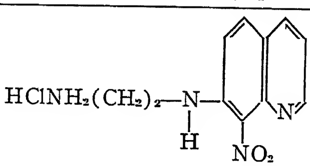
No.	Compound	Maximal Tolerated Dose in Grams
570	 5-Nitro-8-(β-aminoethylamino)-quinoline HCl	0.0005-0.001
576	 5-Amino-8-(β-aminoethylamino)-quinoline HCl	0.00025-0.0005
571	 5-Nitro-6-(β-aminoethylamino)-quinoline HCl	0.0005-0.001
574	 5-Amino-6-(β-aminoethylamino)-quinoline HCl	0.0025-0.004
572	 7-(β-Aminoethylamino)-8-nitroquinoline HCl	0.005-0.008

TABLE 12.—*Chemical Constitution and Toxicity of Amino and Nitro Quinoline Derivatives.*—(Continued)

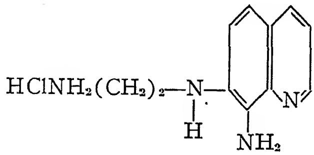
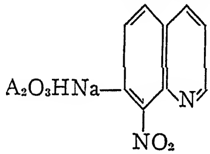
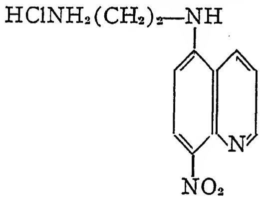
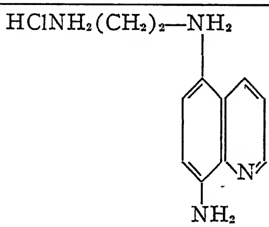
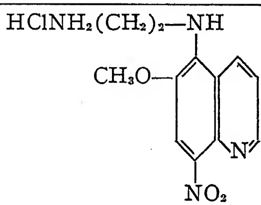
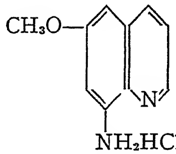
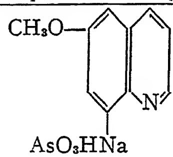
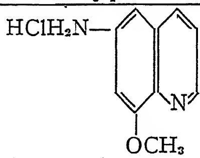
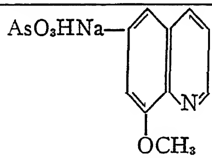
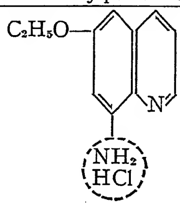
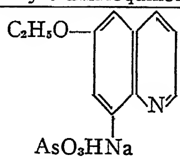
No.	Compound	Maximal Tolerated Dose in Grams
575	 7-(β-Aminoethylamino)-8-aminoquinoline HCl	0.005- 0.008
596	 Sod. 8-Nitroquinoline-7-arsonate	0.003- 0.005
573	 5-(β-Aminoethylamino)-8-nitroquinoline HCl	0.0025- 0.005
582	 5-(β-Aminoethylamino)-8-aminoquinoline HCl	0.0005
593	 5-(β-Aminoethylamino)-6-methoxy-8-nitroquinoline HCl	0.002

TABLE 12.—*Chemical Constitution and Toxicity of Amino and Nitro Quinoline Derivatives.*—(Continued)

No.	Compound	Maximal Tolerated Dose in Grams
587	 6-Methoxy-8-aminoquinolineHCl (plasmoquine base)	0.0005
588	 Sod. 6-Methoxyquinoline-8-arsonate	0.003-0.005
597	 6-Amino-8-methoxyquinoline HCl	0.010
598	 Sodium 8-Methoxyquinoline-6-arsonate	0.005-0.008
600	 6-Ethoxy-8-aminoquinolineHCl	0.003-0.005
601	 Sodium 6-Ethoxyquinoline-8-arsonate	0.003-0.005

but with negative results, although they showed some therapeutic value in birds. No. 600 in doses of 0.0005 gram delayed the infection for five days and after the administration of the third dose it caused a reduction of the number of parasites.

Chapter VIII.

Quinine Group.

Chemistry of Quinine Alkaloids.

Quinine is one of the alkaloids of cinchona bark. The cinchona tree was originally a native of the mountain sides of the South American Cordilleras, where it grew in regions 1200 to 3500 meters above sea level in Caracas, Bolivia, New Granada, Ecuador and Peru. It is at present cultivated most successfully in other countries such as Java, Batavia, the Indies, Ceylon and in some other places. In recent years more than 95 per cent of the total world production of the alkaloids has been exported from Java. At present quinine is prepared mostly from *Cinchona ledgeriana* grafted on *Cinchona succirubra*. W. F. Dawson (**1930**) gives the alkaloid content of cinchona bark as follows:

Alkaloid	Per Cent
Quinine	4.143 (4.4-5.1)
Cinchonidine	0.542 (0.4-0.6)
Cinchonine	0.381 (0.3-0.4)
Quinidine	0.170 (0.16-0.2)
Amorphous alkaloids	0.888 (0.8-1.6)

(The figures in brackets give the values of *Cinchona ledgeriana.*)

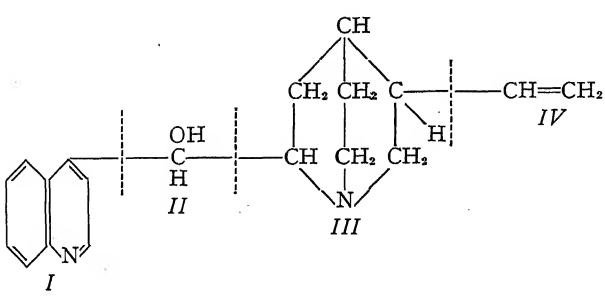
Most of the alkaloid is recovered from the bark of the roots, trunk and branches. The bark of the root has the highest content of total alkaloids; the bark of the trunk the highest content of quinine. The alkaloids are mostly stored in the parenchyma of the bark; they are absent from the cambium and the tubular system. The flowers, the seeds and the fruits contain little if any. The content of the leaves varies considerably. The question whether the alkaloids are synthesized directly or whether they are metabolic waste products is not settled; many observations are in favor of the latter assumption. The alkaloid content of the bark varies widely between 1 and 17 per cent. An extensive review of the literature is given by C. Wehmer, "Die Pflanzenstoffe," G. Fischer, Jena, **1911**.

The name Quina is of Inca origin and means bark; the name Cinchona was chosen by Linné for this family of plants in memory of Countess de Chinchon, the wife of the Viceroy of Peru, who in 1638 was cured from a fever by the powdered bark which was therefore also called "polvo de la condesa." It was only a hundred years later that the tree itself became known to Europeans.

Quinine and cinchonine, the most important alkaloids, were first isolated by Pelletier and Caventou (**1820**). Fourcroy and later Vauquelin had isolated an impure mixture about 30 years before. Quinidine was isolated by Henry and Delondre (**1833**), cinchonidine by Winkler (**1848**), cinchotine by Caventou and Willm (**1869**), quinamine by Hesse (**1872**), who also isolated conchinamine (**1877**) and cinchamidine (**1881**). In the same year (**1881**) cinchonamine was isolated by Arnaud, hydroquinidine by Forst and Boehringer, and hydroquinine (**1882**) by Hesse. Several other alkaloids were found in the bark of different cinchona species, but only cupreine, isolated by Paul and Cownley (**1884**) from remija bark, is of interest in connection with our problem. Quinicine prepared (**1853**) by L. Pasteur from quinine seems also to be a constituent of certain barks.

These alkaloids and several others in the cinchona bark are bound to different acids such as quinic, quinovic acid and quina and quinova-tannic acids. The quinic acid was discovered by F. C. Hofmann (**1790**) and characterized later as hexahydrotetrahydroxybenzoic acid.

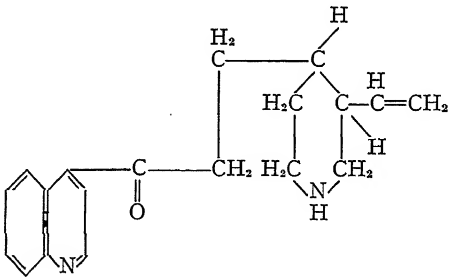
Cinchonine. The empirical formula of cinchonine was established by Skraup (**1879**) as $C_{19}H_{22}N_2O$ and its structural formula was elucidated mainly by the studies of Koenigs, Skraup and Rabe; Rohde and Antonaz (**1907**) assigned to it the following structure:



This alkaloid consists, therefore, of three parts: the quinoline ring (*I*); a complicated complex (*III*) which Koenigs called the quinuclidine group and which contains in meta position to the nitrogen atom a vinyl group (*IV*), and an alcoholic group (*II*) which connects the two radicles and which is in 4- position to the quinoline and in ortho position to the quinuclidine nitrogen.

Cinchonine consists of translucid prisms which sublime at 220° C., melt at 250° C., and volatilize in vacuum without decomposition. It is dextrorotatory, nearly insoluble in water and difficultly soluble in alcohol and ether; the solutions are alkaline, cinchonine having marked dibasic properties. The acid solutions of its salts show blue fluorescence; this is less marked than with quinine (Andant, 1930).

Cinchonicine, prepared in 1853 by Pasteur, is a derivative of this alkaloid and its name was afterwards changed to cinchotoxine at the suggestion of von Miller and Rhode. Since other derivatives of quinine and cupreine of the same type were afterwards also called toxines, this name will be used in the following. Its formula is according to Rabe:



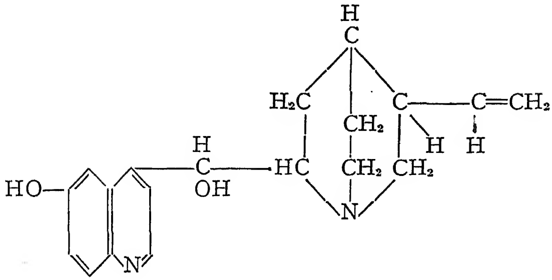
Cinchonidine is probably stereoisomeric with cinchonine since it gives the same decomposition products. It crystallizes from diluted alcohol in prisms melting at 207° C. It is levorotatory, difficultly soluble in water, easily soluble in alcohol and chloroform. It shows fluorescence like cinchonine.

Cinchotine (hydrocinchonine) forms dextrorotatory prisms melting at 286° C.

Cinchamidine (hydrocinchonidine) forms levorotatory prisms melting at 230° C.

Cinchonamine forms dextrorotatory needles melting at 184° C.

Cupreine, $C_{19}H_{22}N_2O_2$, has the structural formula:



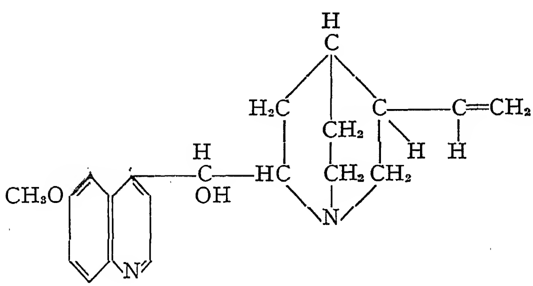
It differs from cinchonine by having a hydroxy group in 6-position of the quinoline ring, which produces the phenol-like character, on account of which it is soluble in alkalies. Having two free hydroxy groups it forms esters with two molecules of acid. Cupreine crystallizes in prisms which melt at 198° C. when water-free. It is easily soluble in alcohol but with difficulty in ether and chloroform.

Apoquinine is an isomer of cupreine prepared from quinine with hydrochloric acid at an elevated temperature. Its structural formula is unknown. It consists of a white powder, is levorotatory and melts at 210° C. (Miura, 1930).

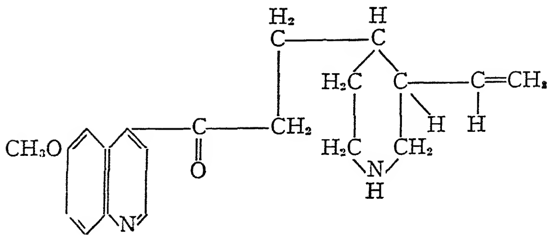
Quinamine, dihydrocupreine ($C_{19}H_{24}N_2O_2$), is dextrorotatory and melts at 172° C.

Conchinamine is the optical isomer of the former, being levorotatory; it melts at 123° C.

Quinine ($C_{20}H_{24}N_2O_2$) has, according to Rohde and Antonaz, the following structural formula:



It is, therefore, the methyl ether of cupreine or the 6-methoxy cinchonine. As in cinchonine the nucleidine ring may be split by treatment with acids with the formation of quinicine (Pasteur) or quinotoxine.



Although the chemical structure of quinine seems to be fairly well established, the synthesis from comparatively simple compounds has not yet been accomplished. Grimaux and Arnaud have, however, succeeded in preparing quinine from cupreine.

Quinine is usually obtained in form of a crystalline powder containing three molecules of water of crystallization and melting at 57° C. The anhydrous and amorphous preparation is obtained by precipitation of the salt solution by means of alkali; this amorphous material melts at 57° C. It is difficultly soluble in water, petroleum-ether and benzene, better in chloroform and easily in alcohol and ether. The solutions are levorotatory, alkaline, and taste intensely bitter. The relation between optical rotation and pH of the solutions has been studied by Dietzel and Soellner (**1930**). The solutions of several salts show fluorescence. This has been studied recently more closely by Andant (**1930**). Like cinchonine it is a dibasic compound, forming salts with two molecules of acid. According to Grimaux and Laborde (**1892**) the hydrochlorsulfate is especially useful because it is soluble in its own weight of water, so that it can be easily injected, being at the same time also less painful than the other salts. It crystallizes with two molecules of water of crystallization, these crystals being very dense; it may, therefore, be pressed into very small tablets, thus facilitating the administration. For identification tests, compare Rosenthaler, "Der Nachweis organischer Verbindungen," Stuttgart, Ferdinand Enke, **1923**, p. 774.

The characteristic groups of the quinine molecule are the methoxy group in 6- position in the quinoline ring, the secondary alcohol group between the quinoline ring and the third essential part, the quinuclidine group, containing a vinyl group in meta position.

Quinidine ($C_{20}H_{24}N_2O_2$) is the optical isomer of quinine, and gives the same reactions and the same quinotoxine as the latter and therefore the difference between the two consists presumably

in the position of the alcoholic hydroxy group in regard to the quinoline ring, as recently demonstrated by Emde (**1932**). It is slightly soluble in water, soluble with difficulty in chloroform, and freely in alcohol and ether. The anhydrous compound melts at 171° C. The solutions of its salts are dextrorotatory. The acid solutions of its salts show fluorescence like quinine. The substance was first described by van Heyningen in 1848 under the name of betaquinine; in 1853 it was prepared by Pasteur and called quinidine; Hesse (**1868**) proposed the name conchinine, Hlasiwitz (**1851**) cinchotine, and Kerner (**1862**) β-chinidine.

The two hydrogenated alkaloids *hydroquinine* and *hydroquinidine* contain in the quinuclidine ring an ethyl group instead of the vinyl side chain, which would explain their resistance towards oxidizing agents such as potassium permanganate. Both compounds can also be prepared by the hydrogenation of quinine.

Hydroquinine crystallizes with two molecules of water, it is levorotatory and the anhydrous compound melts at 172° C.

Hydroquinidine is dextrorotatory and melts, when anhydrous, at 168° C. Both compounds have been synthesized by Rabe, Huntenberg, Schultze and Volger (**1931**).

Pharmacology of Quinine Alkaloids.

Cinchonine.

Cinchonine is only slightly bitter. According to Giemsa (**1914**) it is less effective *against malaria* than quinine, which was confirmed by Meldolesi (**1925**) and by Sergent and Catanei (**1926**). According to Piccinini (**1926**), confirmed by Ohlson (**1930**), the inhibiting action on amylotic processes is less marked than that of quinine.

Concentrations of 1:1000 to 1:2000 reduce the frequency of the *heart rhythm* but have very little or no effect on the volume of the isolated frog heart (Santesson, **1892**). Fredericq found concentrations of from 0.5:1000 to 5:1000 to be toxic for the turtle heart. Meldolesi (**1925**) believed that it is more toxic for the heart than quinine. Chopra, Dikshit and David (**1928**) found that it stimulates the auricular contractions, presumably on account of a depression of the inhibitory mechanism, and that by reducing the irritability of the myocardium it depresses the ventricle. They also found that the refractory period is not notably affected. Santesson (**1892**) assumed that it affects the motor ganglia more than the cardiac muscle.

Cinchonine dilates the *blood vessels* as observed by Kobert (1887) in organs perfused with concentrations of from 0.1 to 0.3: 1000; this was confirmed in the frog by Stake (1929), who found that even small doses of cinchonine reverse completely the vasoconstriction produced by epinephrine. Chopra, Dikshit and Pillai (1929) believed that the fall of blood pressure observed in rabbits after intravenous injection of 25 mg. per kilogram is due to a depression of the vasomotor center and of the peripheral vasomotor endings, which is most marked in the splanchnic area, as shown by the rise of the spleen volume and an increased venous flow which may produce a secondary vasoconstriction of the blood vessels of the skin. They assumed that a direct depression of the muscle fibers of the vessels is not the main factor in the phenomenon.

In contrast to quinine, cinchonine does not prevent the emigration of leucocytes (Ikeda, 1926). This is paralleled by the findings of Shaw (1928) that the absence of the methoxy group reduces the partition coefficient of these compounds.

On *striated muscle* Santesson (1892) found it to be slightly less effective than quinine. Heffter (1893) found the lactic acid production considerably reduced in cinchonine-poisoned muscles, which may be explained by interference with the oxidative processes. According to Veley and Waller (1909) its depressant action is about one-fourth that of quinine.

In regard to the stimulation of the *uterus,* Hale (1915) found it to be more effective than quinine. This seems to be confirmed by the experiments of Chopra, Dikshit and David (1928).

The *convulsant action* of cinchonine seems to be more marked than that of quinine (Albertoni, 1882; Heffter, 1893; Weber, 1908). The toxicity, however, seems to be somewhat lower than that of cinchonidine. According to Langlois (1893) the convulsant dose is 0.06 gram per kilogram dog. Clerc, Pezzi and Brochaud (1923) believed it to be less toxic for the vagus center than quinine. W. Rosenstein (1900) studied nitrogen-substituted cinchonine derivatives, in particular the chloromethylate, and compared the action of the latter with that of cinchonine. While the convulsant action is predominant with cinchonine, the chloromethylate shows the characteristics of a quaternary base producing peripheral motor paralysis, the methyl cinchonine still being of the convulsant type of nerve poisons. From this he concludes

that the curare action is not due to the substitution of alkyl radicles, but that it only can be produced by the change to a quaternary base. This is in contradiction with Santesson's report (1895) that methyl and amylcinchonine have a curare-like action. Hildebrandt (1908) found that intravenous injection of cinchonine iodomethylate causes a considerable fall of blood pressure, the pulse becoming small and impossible to count.

Cinchonamine is an isomer of cinchonine; according to Ellram (1901) it is a weak protoplasmic poison which paralyzes the nerves and the muscles of all cold-blooded animals. In mammals it stimulates the cortex of the brain.

Cinchonidine is a levorotatory isomer of cinchonine. According to Piccinini (1926) it is more effective in inhibiting amylotic processes than cinchonamine. Meldolesi (1925) found it is less effective against *malaria* than quinine, but Sergent and Catanei (1926) consider it more effective than cinchonine, approaching nearer to quinine in its efficiency. It lowers the blood sugar level like quinine, although only in larger doses, but the effect is said to be more distinct than with the latter (Fujino, 1930).

Its *cardiac* action is very similar to that of quinine, a concentration of 1:1000 reducing both frequency and volume of the pulse beat. It has the same beneficent effect on cardiac irregularities and therefore is evidently more effective than cinchonine. According to Fredericq (1913) concentrations of 2.5:1000 are toxic for the isolated turtle heart. Chopra, Dikshit and David (1928) consider it to be more toxic for the heart than cinchonine. According to Chopra, Dikshit and Pillai (1929) it affects the blood pressure in the same manner as cinchonine. It also acts upon *striated muscle* in the same way as cinchonine [Santesson (1892), Veley and Waller (1909)]. Albertoni found that it causes convulsions mainly by action on the brain and the spinal cord like cinchonamine; according to Langlois (1893) it is less toxic than cinchonine, the convulsant dose being 0.08 gram per kilogram as compared with 0.06 gram per kilogram for cinchonine.

A comparison of the pharmacologic action of the two isomers reveals that the levorotatory compound is generally more effective in regard to the antiferment, antimalarial, the cardiac and the convulsant action.

Cupreine.

Cupreine contains one hydroxyl group in the 6- position in the quinoline ring. According to Grimaux, Laborde and Bourru (1894) it causes prolonged anesthesia when injected hypodermically. It is half as toxic as quinine, less convulsant than cinchonine, and causes slight reduction of the temperature. Grimaux and his co-workers found it inferior to quinine in antimalarial action, which was later confirmed by Giemsa (1914).

From this it appears that the introduction of the hydroxy group in the 6- position in the quinoline ring does not materially improve the antimalarial action, but that it reduces the toxicity and especially the convulsant action.

Apoquinine has not been studied extensively. Okamoto and Sogen (1930) stated that the instillation of a 1.33 per cent solution into the rabbit eye caused marked hyperemia and edematous swelling of the conjunctiva and increased lacrymation but no anesthesia.

Miura (1930) prepared the methyl, ethyl and isoamylether of apoquinine.

Methylapoquinine is said to be a more powerful antiseptic than quinine, being at the same time less toxic for mammals (Okamoto, 1930). It causes some irritation when instilled into the rabbit eye and has some local anesthetic action, which is said to be superior to that of methylhydrocupreine (Okamoto and Sogen, 1930).

Ethylapoquinine has a marked germicidal action for pneumococci. Okamoto (1930) found it in this respect two to four times as potent as optoquine after two to twenty-four hours' contact. He found it less toxic than ethylhydrocupreine for mammals and of distinct therapeutic value in mice infected with pneumococci. According to Okamoto and Sogen (1930) it has some local anesthetic properties but is also somewhat irritant when instilled into the eye. Miura and Sogen (1931) found that it is four times more effective than optoquine in killing pneumococci in 10 per cent serum bouillon.

Ethylapoquinidine was found to be eighty times less effective than the apoquinine derivative and **ethyldehydroapoquinine** with a triple bond in the side chain is also less effective but still twice as potent as optoquine. According to Matsuda (1931)

ethylapoquinine has a very marked curative action on pneumococci infections of the rabbit cornea. Instillation of 1 and 2 per cent solutions for from two to three minutes three times daily resulted in complete cure in 91.3 per cent (23 experiments).

Isoamylapoquinine is about as effective as isoamylhydrocupreine in its antiseptic action against streptococci; against staphylococci it was found to be twice as potent as the corresponding hydrocupreine derivative, being less toxic for mice than the latter. Its local anesthetic effect is 28 times stronger than that of cocaine, but it also causes some irritation.

Quinine.

The antiseptic action of quinine was recognized early. The fact that quinine is a protoplasmic poison was pointed out by Pringle (**1765**) when he found that the powder or decoction of cinchona prevented the putrefaction of meat. These observations were repeatedly confirmed by others, and Binz (**1868**) noted that concentrations of 1:20,000 killed paramecia within some hours. He also observed differences in the susceptibility of different species and noticed that high dilutions may produce stimulation instead of depression. Thus he conceived the idea of the etiotropic action of quinine in malaria which was later confirmed by the discovery of the parasites by Laveran (**1884**). The antiseptic properties of quinine solutions came to be generally accepted. As early as 1888 Marcacci discovered that quinine solutions, ineffective in the dark, prevent the germination of seeds and the development of frog eggs when exposed to light. The antiseptic action of quinine was confirmed by Bokorny (**1892**), Grethe (**1896**), Taylor (**1915**), Dixon and Premankur (**1927**), Busk (**1906**) and others. Samura (**1930**) found that quinine, like quinidine and more than cinchonine, cinchonidine and optoquine, inhibits the growth of fibroblasts in cultures, proportional to the concentration of the drug. Under the influence of quinine the cells in the zone of growth showed irregular polygonal rounded forms, and fat droplets and vacuoles could be detected in the cytoplasm. Busk (**1906**) found that the addition of serum reduces considerably the antiseptic action of quinine. Recently the difference in the toxicity of quinine solutions in the light and in the dark has aroused much interest, as indicated by the publications of Feiler (**1928**), Milanesi (**1928**) and Roskin and Romanowa (**1929**); but other factors also seem to play an impor-

tant rôle. Troendle (1920) studied the penetration of quinine salts into *Spirogyra majusculata* and *Spirogyra X* and found that only the free base, in the case of salts only the alkaloid liberated by hydrolytic dissociation, could penetrate and that reduction of hydrolysis by the addition of acids reduced the penetration.

Ash and Myer Solis-Cohn (1929) found that the germicidal action of quinine against pneumococci increases with increased alkalinity. This effect is manifested at the pH of normal blood (pH 7.4) and more alkaline solutions were found to be more effective. Higher dilutions of quinine were found to stimulate the growth of the organisms. This was confirmed by Feiler (1928), who found that concentrations of $1:10^{-7.5}$ stimulate the growth of pneumococci and favor their proliferation. Short exposure to more concentrated solutions (1 : 30,000) acts in the same direction.

Giemsa and von Prowazek (1908) studied the morphological changes of infusoria under the influence of quinine. They observed the appearance of droplets in the protoplasm, indicating a change of the lipoids of the cells. The nuclei showed precipitation and the pulsations of the vacuoles were reduced. The movements which were first stimulated became more and more depressed. Prowazek assumed that the alkaloid is bound by the protoplasm and Moldovan (1912) considered the interference with the oxygen metabolism as the final cause of death.

Clinically the antiseptic properties of quinine solutions have been utilized extensively. Of the more recent publications on the subject we may mention the paper of Hartung (1911) on the treatment of infectious colds with quinine solutions, Taylor (1915), who recommends quinine solution as wound dressing, and McDonald (1915), who recommends its use for irrigation of the bladder. Moon (1913) claimed benefit from the administration of quinine in rabies, but later experiments were less successful and Krumwiede and Mann (1915) were unable to find any effect of quinine on rabies in rabbits and in dogs.

It is questionable whether the *antimalarial properties* of quinine were known to the natives of South America prior to the Spanish conquest, and it appears that its use in malaria occurred accidentally. The first case reported in the literature is probably that of the Countess of Chinchon in 1638; however, eight years prior the Spanish corregidor of Loxa, Don Juan Lopez de

Canizaro, had been cured. Since that time the drug has been used extensively in the treatment of malaria and of other fevers.

Comparative studies on the efficiency in this respect of quinine and other quinine alkaloids have been made repeatedly. The first extensive study was that of the "Madras Cinchona Commission" published in 1867/68. The commission accorded the same rank to quinidine as to quinine, they found cinchonidine only slightly less efficacious and cinchonine considerably inferior to the other alkaloids. This work was done before the malaria parasite was discovered, and, therefore, neither the diagnosis nor the cure was absolutely certain; the purity of the preparations used may also not have been of the present high standard.

The value of quinine as a prophylactic in malaria was discussed extensively by Acton (1920/21) and the whole question of the malaria treatment with quinine was reviewed by Dawson (1930). The lack of effect of quinine on the sporozoic stage, which has already been discussed, renders such prophylaxis rather uncertain, as has been demonstrated by the experiment of Yorke and Macfie (1924). They showed that the oral administration of small quantities of quinine immediately before, during, or just after the infection with malaria parasites does not constantly prevent the experimental infection.

Opinions on the subject of *the mechanism of action of quinine in malaria* do not agree. W. Kirschbaum (1923) reported that solutions of quinine hydrochloride (1 : 5000) in normal saline or in dextrose solution mixed with equal parts of tertiana blood remained infectious after incubation of from 5 to 24 hours at 38° C. Muehlens and Kirschbaum (1924) repeated these experiments and found that only after an incubation period of 24 hours and more the inoculation test became negative. Therefore they concluded that quinine does not act on the plasmodia directly but by mobilizing the defense mechanism of the host. This assumption was contradicted by Giemsa (1927), who claimed that quinine acts directly on plasmodia and that it is unable to produce antimalarial substances in the host. He assumed that the decomposition products of the parasites may give rise to the mobilization of the self-defense mechanism. Loewenstein (1917) assumed that with parenteral but not with oral administration quinine has a two-fold effect, one starting after 24 hours, reaching a moderate degree of short duration, and one which becomes manifest only after 20 days and which causes a more marked and lasting

effect on the organism. During this period the excretion of quinine is considerably reduced, indicating an increased destruction. Loewenstein (1917) claimed also that quinine is more effective on those forms of the parasite which are rich in protoplasm and comparatively poor in chromatin. Schilling and Schulze (1930) injected intramuscularly in paralytic patients two times 1 gram of quinine seventy-two hours after the inoculation with tertian malaria, i.e., at a time when only few parasites were in the peripheral blood. They found that this dose prevented the infection. On account of the small number of parasites in the peripheral blood it is not very likely that antigenic or protective substances had been formed in the blood during that time and that quinine mobilizes the self-defense mechanism, nor that the decomposition products of the parasites can be credited with this effect. However, it is peculiar that quinine does not prevent the "prodromal fever" which starts on the fourth day after the inoculation and which only on the sixth or seventh day passes into the typical malaria paroxysm. Borchardt (1930) determined the minimal dose of quinine which killed *Plasmodia praecox* after 5 hours contact with the plasmodia prior to the inoculation of birds. He found that 0.5 mg. of quinine hydrochloride in 1 cc. of the blood-normal saline mixture was the minimal effective concentration, and he assumed a direct action on the plasmodia. Bass (1922) studied the effect of quinine on cultures of *Plasmodium falciparum* and found that therapeutic concentrations of quinine hydrochloride inhibit the growth and change the staining properties of the plasmodia after incubation for 5 hours. After 29 hours the plasmodia were evidently dead. We noted above under plasmoquine that the action of quinine on the plasmodia and their different forms is not uniform and that quinine does not affect the gametocytes but only the schizonts. This is illustrated by an experiment of James, Nicol and Shute (1927-28). They found that the injection into man of sporocytes obtained from infected mosquitoes causes malaria. They then placed mosquitoes infected with *Plasmodium vivax* in solutions of quinine bisulfate 1 : 5000 made up with human blood serum. In this solution they dissected and teased up the salivary glands and after 15 minutes 1 cc. of this solution was injected subcutaneously into a human being. At the end of 10 days the patient developed a malaria paroxysm and the plasmodia were found in the blood. This experiment

indicates that not all the sporocytes present in the quinine-blood serum mixture had been killed during the 15-minute contact.

Morgenroth (**1918**) had assumed that quinine is concentrated on the surface of the red blood cells rendering these impermeable to the parasites. But Giemsa (**1927**) pointed out that the distribution of the drug in the blood between the serum and the erythrocytes does not warrant such an assumption and furthermore that the amount of quinine in circulation decreases so rapidly that no lasting protection can be expected by such a mechanism. Hegner, Shaw and Manwell (**1928**) stated that only those quinine derivatives have antimalarial properties which are soluble in red blood cells. This may indicate that the site of the action is in the interior of the cell. Kehar (**1931**) studied the penetration of quinine and other cinchona alkaloids into gels, and found that this is accelerated by acids and alkalies, while neutral salts have no effect; monobasic organic acids vary in their effect depending on the length of the carbon chain; dibasic and tribasic organic acids accelerate the diffusion and it appears that this is greater the lower the molecular weight of the compound. He also found the interesting fact that the penetration of the cinchona alkaloids was enhanced by the presence of plasmoquine, which may explain the synergistic action. In the treatment of paralytic patients inoculated with malaria, Kroo and Schultz (**1927**) observed that the intravenous administration of diluted solutions of quinine and ethylurethane (quinine hydrochloride and urethane āā 0.2 gram in 200 cc. of water) was more effective in reducing the number of fever-free days than a concentrated solution containing the same doses in 0.9 cc. of water.

The *administration of quinine in the treatment of malaria* has been closely linked to the biological cycles which the plasmodia undergo in the human organism. Several systems of administration have been worked out from this point of view. All seem to have been successful, provided sufficiently large doses were given. Maxcy (**1930**) gives a review of this subject: The experiences of the world war indicate that the oral administration of 0.6 gram two times daily causes disappearance of the parasites from the peripheral circulation and abolishes the fever. There is, however, a marked difference between a clinical recovery and a parasitic cure, the latter implying complete destruction of the parasites in the body so that relapses cannot occur. This goal seems to be seldom reached with such doses and a few parasites may

escape destruction, causing relapses after the treatment has been discontinued. It appears that the malaria parasite, unlike some other microorganisms (trypanosoma), do not acquire a fastness towards the specific drug. Recent infections generally respond more readily to quinine treatment than chronic forms or repeated infections. It is apparently immaterial when the drug is administered in reference to the chill, the time of sporulation of the parasites. Sinton (**1931**) stated that the dose of quinine needed to control the clinical manifestations of tertiana is smaller than that needed in malignant tertiana, because quinine has an elective action for the trophozoites of this form. A greater dose is required in quartan malaria because the plasmodia are more resistant to quinine than the other two forms and because relapses may occur for a long time. While 1.2 grams daily may be sufficient to control benign tertiana (although a prompter reaction is probably obtained with a daily dose of 2.0 grams), a daily dose of not less than 2 grams is required during the acute stage of quartan and malign tertian infections. Sinton therefore recommends for routine treatment 2.0 grams of quinine daily in the acute stage of malaria irrespective of the species of the parasite; especially because the large doses are more effective in causing the disappearance of the parasites from the peripheral blood. It appears that the rate of the cure in malaria rises with the duration of the quinine treatment, but in benign tertian malaria as in other forms this increase in rate is neither directly proportional to the length of the treatment nor to the total amount of quinine given. It seems probable, however, that the continued use of larger doses over a long period may be harmful to the human organism and may even interfere with the process of permanent cure. In primary infections 2.0 grams daily for a week is sufficient as a rule, and this treatment is said to cure 70 per cent of fresh malaria infections. Manson-Bahr (**1931**) still adheres to the older theory that quinine should be given when the acute paroxysm is declining, for at that moment the plasmodia have sporulated and the merozoites are free in the blood plasma. He gives the 2-gram dose only for 4 days and then reduces it to 1.2 gram for the following week and administers only 0.6 gram daily during the following 6 weeks. In subtertian infections the parasites are characterized by a more rapid multiplication and reproduction by sporulation in the capillaries. While the trophozoites are extremely susceptible to quinine, the sexual forms or crescents are

quite resistant. Escher and Villequer (1931) advocated the use of intravenous injections in the treatment of pernicious malaria. They employed a solution of from 0.5 to 0.8 gram of quinine hydrochloride in 250 cc. of normal saline with the addition of 1 mg. of epinephrine, to be injected within one-half hour. They also used a more concentrated solution containing 0.3 to 0.5 gram in 10 cc. of water with the addition of epinephrine. Prior to the injection 10 cc. of blood is withdrawn and mixed in the syringe, and this mixture is then injected during a period of from 5 to 10 minutes. From 5 to 6 such injections are given on subsequent or alternating days and are preferably combined with the oral administration of doses of 0.6 to 1.0 gram. Senility and cardiac diseases are contraindications for this form of treatment. As a whole the effect of intravenous administration of quinine seems to be not superior to that of oral administration (K. F. Maxcy, 1928). The limitations and dangers of this method were discussed by Maxcy (1922).

The *inhibiting action of quinine on ferments* has been studied quite extensively. The inhibition of the fermentation of yeast was already observed by Liebig (1870) and by Kerner (1870). Recently Rona and Nicolai (1927) showed that the effect is most marked at a pH at which the alkaloidal salt is completely dissociated. Binz (1873) found that it prevents the guaiac reaction of blood, which may be interpreted as a toxic effect on the oxidase, but Johannessohn (1918) stated that therapeutic doses do not affect the oxidase reaction in the living organism. Nasse (1875) found that it reduces the invertase reaction considerably, but increases the action of saliva very noticeably, and that of the pancreas slightly. Laqueur (1906) in his extensive study on the action of quinine on ferments, found that it generally decreases the action of the autolytic ferments of the liver in rabbits but not in dogs. Rosenthal and Lipschitz (1926) found no distinct difference between both species. Quinine increases the pepsin action and in small concentrations also the catalase and oxidase reaction of the blood, while the depressant action on the latter two starts with concentrations of 0.5 per cent. The activity of rennet and lipase is generally depressed by quinine. Rona and Bloch (1920) found later that the inhibiting action on invertase increases markedly in inverse ratio to the hydrogen ion concentration, corresponding to the ionization of the quinine salts. Only the free base has toxic properties which are completely reversible.

Rona and Reinicke (1924) claimed that the same holds true for the effect of quinine on lipase. In animal serum quinine is in this respect from 100 to 1000 times less active than in human serum, but this protective action of animal serum cannot be transferred to human serum by mixing the latter with very resistant animal serum. The reason for this resistance has not been elucidated. Piccinini (1926) found that great dilutions (from 1:2000 to 1:500,000) stimulate the amylotic reaction while higher concentrations are inhibiting; but Ohlson (1930) could find no indication for a stimulation by small concentrations. Smorodinzew (1928) found that quinine hydrochloride in concentrations of 0.2 per cent does not affect the digestion of edestin by pepsin. A higher concentration of 0.5 per cent may produce some inhibition which may be antagonized by slight increase of the acidity. The moderate inhibiting effect is said to be entirely due to a shifting of the pH towards the alkaline side by the alkaloid. Sabatani (1928) injected intravenously from 0.024 to 0.5 gram per kilogram into young rabbits but noticed no uniform effect on the catalase action, although a slight increase was found in most cases.

The fate of quinine in the metabolism. The inhibitory action of quinine on the activity of ferments is also reflected in its effect on the metabolism. As early as 1874 von Boeck and Bauer found that quinine depresses the cellular functions involved in the nitrogen metabolism and that it reduces also the gas metabolism. Three years later A. Hoffmann (1877) found that quinine inhibits the formation of hippuric acid after the administration of glycine and attributed this to cell injury. Prior (1884) found that the total nitrogen in the urine is decreased after quinine and pointed out that this is not due to difficulties in the elimination but to decreased nitrogen metabolism. Similar results were reported by Kumagawa (1888). Riddle and Anderson (1918), feeding quinine in small doses to fowls, found that the size of the yolk and of the eggs was reduced and they believed this to be due to the decreased nitrogen metabolism. Later Behrle and Riddle (1919) found that under the influence of quinine less nitrogen is released by the albumen-secreting glands of the oviduct, which proves the correctness of their former statement. Hardikar (1924) pointed out that the older work on the effect of quinine on the metabolism cannot be considered to be reliable, in part because the methods used were inadequate, partly because the subjects under investigation were not in nitrogen equilibrium. He

found that quinine in ordinary doses (in human subjects 1.2 grams per day and in healthy animals, such as dogs and rabbits, in doses up to 50 mg. per kilogram) has no influence on the nitrogen metabolism. This was confirmed by Rosenthal and Lipschitz (**1926**), who found that the effect of quinine on the protein metabolism is not constant and that the metabolism is sometimes increased. Similar results were reported by Chahovitch and Vichnjicht (**1928**) and by Hiramatsu (**1931**), who found that in rabbits small doses of quinine at first increase the nitrogen metabolism and also the quantity of the urine output, and that this is followed by a period of decreased nitrogen excretion. The supposed depressing effect on the nitrogen metabolism has been used by Aoki (**1928**) in the treatment of patients suffering from hyperthyroidism. Loew and Krĕma (**1928**) pointed out that a depression of the metabolism occurs more markedly and more regularly with quinine than with other antipyretics such as antipyrine and pyramidon.

Hughes and Shrivastava (**1927**) found that quinine in antimalarial doses causes a retention of phosphate, which they attributed to interference with the carbohydrate metabolism, as indicated by the fall of the blood sugar level. Loew and Pfeiffer (**1927**) observed also in diabetic patients after the administration of quinine a reduction of the acetone compounds in the urine. Jachia (**1930**) found that quinine in doses of 0.4 to 0.6 gram injected intramuscularly or intravenously into diabetic patients produced hypoglycemia and antiglucosuric action. He believed that this is due to its restraining action on the sympathetic system and to its inhibitory effect on the hepatic cells. From experiments in rabbits Kuno (**1930**) assumed that small doses of quinine always produced hypo- and larger doses hyperglycemia; the latter being absent if the adrenal glands had been excised and the splanchnic nerves divided. From this he concluded that the hyperglycemia is of central origin and secondary to an increased output of epinephrine. Fujino (**1930**) confirmed the findings of Kuno as to the effect of small and large doses on the blood sugar level and found that small doses antagonized the hyperglycemic action of epinephrine. Tatum and Cutting (**1922**) had also observed hyperglycemia after appropriate doses and linked this with a central action of the drug. Paolini (**1928**) reported that in mild and less severe diabetes therapeutic doses of quinine promptly reduce hyperglycemia and glucosuria in man, and improve also

the general condition of the patients; severe cases are more resistant. This action was found to last for one to three hours after the administration of the drug.

According to Hiramatsu (1931) the effect of quinine on the respiratory gas metabolism in rabbits is very small even with large doses, small doses having no effect. Meyer and Reinhold (1926) observed reduction of oxyhemoglobin in tissues by means of spectroscopic measurements and noted after quinine a reduction of the oxygen metabolism. In concentrations corresponding to those obtained with therapeutic doses in man it has little or no effect on the oxygen metabolism of hashed muscle (Senta, 1908). Like other antipyretics the marked antipyretic properties of quinine can be antagonized by diuretics. Averbruck (1930) assumed that this is probably not due to a depression of the peripheral metabolism but rather to a shifting of the distribution of water under the influence of the central action of quinine. Hermann (1931) found that after oral administration of 0.3 gram of quinine to rabbits the ratio of total blood calcium to calcium not bound to proteins in the blood is decreased.

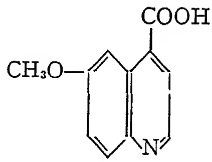
Absorption, distribution and excretion of quinine. Giemsa and Schaumann (1907) found that the absorption of quinine after oral administration takes place mostly in the stomach and the small intestine; the maximal excretion occurs within 12 hours if the drug is taken on an empty stomach, and the excretion is delayed when the drug is given after a meal. Grosser (1908), however, believed that the filling of the stomach at the time of administration is of no importance for the rate of excretion which is always more or less uniform during the first 24 hours. Kleine (1901) had previously stated that the amount of quinine excreted after the administration on a full stomach was smaller than when given on an empty stomach. Hartmann and Zilia (1918) have denied this. The absorption of quinine is distinctly smaller when given as enema than with oral administration. But contrary to the statement of Hartmann and Zilia, Acton and Chopra (1925) found that the administration of alkalies enhances and increased acidity of the stomach reduces the absorption of quinine. This may be explained on the basis of the experiments of Chopra and Choudhurry (1929), who found that the surface tension of quinine solutions decreases with increased alkalinity, resulting in a greater concentration of the drug in the interface of the cell walls. As to the behavior of different quinine salts in this respect no great

difference seems to exist. According to Hockett (1929), they are all precipitated as quinine salts corresponding with the precipitating alkaline salt. This precipitation occurs with different quinine salts at different hydrogenion concentrations which, however, are all within the pH range of the duodenum and the human stomach. Loewenstein and Neuschloss (1917) found that after parenteral treatment with quinine further administration reduces the total excretion. If to such patients the drug is given orally the period of excretion is shortened but the maximal excretion occurs at the same time as with oral administration to normal persons.

As regards to the circulation of quinine in the blood, Giemsa and Schaumann (1907) claimed that the blood contained only very small quantities of the drug and that these are always deposited in the organs before more quinine enters the circulation. This was recently confirmed by Hatcher and Gold (1930). Giemsa believed that the concentration in the blood is too small to warrant a therapeutic action on the parasites and that this occurs in the organs. Hatcher and Weiss (1926) assumed that the fixation of quinine in the capillaries is essential for the destruction of the parasites. As to the distribution of quinine in different organs Giemsa and Schaumann (1907) found that liver, kidney, adrenals and brain contain distinctly more than spleen. Similar results were reported by Baur (1918). Sadler, Dilling and Gemmell (1930) found that after therapeutic doses in obstetrical cases the concentration of quinine in the placenta was highest in about eight hours after the administration and that traces may be present even after 83 hours. Hartmann and Zilia (1918) claimed that the quinine level in the blood varies considerably with different methods of administration. It is maximal with intravenous injection, but in 5 minutes after the injection from 60 to 90 per cent has already disappeared from the circulation. With intramuscular injection the maximal concentration of quinine in the blood is smaller than after intravenous administration but it disappears from the circulation in about the same time with both methods of administration. With subcutaneous injection the absorption may be markedly delayed; Kleine (1901) found quinine at the site of the injection as late as 4 weeks after the administration.

After oral and subcutaneous administration quinine may be detected in both feces and urine. Kaewel and Kuehn (1927),

Smorodinzew (1928) and Stransky (1931) found that following different methods of administration quinine is excreted with the bile of dogs. Leineweber (1883), Kandidoff (1893) and Bongers (1895) claimed that after subcutaneous administration quinine is excreted into the stomach because they could isolate it from the vomited gastric contents. However, this does not exclude that the quinine discovered was excreted with the bile into the intestinal tract. Kerner (1870) isolated a compound from the urine which he considered to be dihydroxyquinine. He thought that this compound was identical with one obtained from quinine by oxidation with permanganate. Halberkann (1919) believed that it was identical with the quitenine of Skraup, that it was presumably formed during the analytical procedure by oxidation with nitric acid and that it was not a metabolic product of quinine. Nierenstein (1919) claimed to have isolated quitenine from urine obtained during the first 2 or 3 hours after the therapeutic dose of quinine by fractional crystallization of the precipitate obtained with picric acid. It seems possible, however, that the drug used was not free of quitenine, on account of the quinine shortage during the world war. The same author reported also having isolated from the urine of black-water fever patients a compound, hemoquinic acid, to which he ascribes the following formula and which appears to be identical with quininic acid:



This compound forms well defined crystals melting at 183° C. with the evolution of carbon dioxide. He stated that this compound has marked hemolytic properties for human and sheep blood-corpuscles and correlated this with the symptoms of this disease. In the isolation, concentrated hydrochloric acid, phosphotungstic acid and barium or sodium hydroxide were used, and since no control experiments were made with urine of normal persons containing quinine, it appears possible that this compound was formed during the process of isolation. Merkel (1884) reported from 12 to 14 per cent as completely destroyed in the organism and the remainder excreted with urine and the feces. Schmitz (1907) found a urinary excretion of only 26 to 30 per

cent of the quantity of quinine given orally. Similar findings were previously given by Kleine (1901), who stated that with smaller doses comparatively more is excreted with the urine. This was later confirmed by Giemsa and Schaumann (1907), who believed that a greater portion of larger doses is destroyed in the organism. Similar results were reported by Grosser (1908), who showed that the liver destroys quinine and that abnormally high urinary excretion would, therefore, indicate an inefficient functioning of the liver. This was also the conclusion of Porak (1918), who noted an increased excretion of quinine in patients suffering from hypertrophic liver; and the same opinion was expressed more recently by Acton and Chopra (1925). Hartmann and Zilia (1918), Halberkann (1919) and Kuester (1919) concluded that the excretion in normal persons and in those habituated to the use of quinine is the same. The course of excretion varies with the method of administration. Nishi (1909) claimed that with oral administration it starts in about half an hour and is practically finished within 72 hours, traces being excreted for some time longer. After the oral administration of 3 times 0.6 gram to parturient women, Sadler, Dilling and Gemmell (1930) found the maximal concentration in the urine to occur from 6 to 12 hours after the administration, the total quantity excreted being about 13 per cent of the amount administered. The amount excreted in the feces after parenteral administration is much smaller than in the urine. Small quantities of quinine are also excreted with the saliva as mentioned by Kunkel and recently confirmed by Fourment and Hermann (1930). The excretion with sweat and milk seems doubtful. Fourment and Hermann also stated that the excretion with bile is more marked.

The effect of quinine on the circulation. According to Santesson (1892) quinine reduces the rate and the volume of the pulse and depresses the absolute energy of the heart, by increasing the refractory period of the heart muscle. Fredericq (1913) found that a concentration of 4:1000 arrests the turtle heart, 2:1000 and 1:1000 develop gradual depression followed by arrest. Similar results were recently reported by Eisenmeyer and Quinke (1929) on the isolated frog heart. Niederehe (1918) found that 0.02 gram produces an increase of amplitude of 27 per cent and increase of rate of 30 per cent in rabbits. Like quinidine it also stops cardiac fibrillation but according to de Boer (1922) it is of permanent value only when the metabolic con-

ditions of the muscle are still fairly good. Okamoto and Miura (1928) also believe that it is inferior to quinidine in this respect. The effect on the heart with systemic administration varies very much with the dose. After doses of 7 mg. per kilogram, Clerc and Pezzi (1923), like Niederehe (1918), observed in rabbits tachycardia which they believed due to stimulation of the accelerator nerve, while larger doses depress the vagus center. They confirmed also the curative value in auricular fibrillation. On the other hand, Bush (1920) had previously observed stimulation of the cardio-inhibitory center by perfusion of the medulla of the turtle. Clerc and Deschamps (1923) found that it has a negative chronotropic and bathmotropic action in dogs, in that it diminishes the rate and renders the heart less sensitive to stimuli and reduces the contractility of the myocardium. With therapeutic doses Halsey, Chapman, Reynolds and Blackberg (1927) noted an increase of the cardiac output. Kikuchi (1928) pointed out that small doses increase and large doses decrease the absolute pressure of the heart. According to Junkmann (1925) the depressant effect of quinine on the cardiac muscle may be antagonized to a certain extent by the administration of digitalis.

As early as 1884 Prior mentioned dilatation of the kidney vessels by quinine. This *vasomotor action* was also noted by Kobert (1887) in organ perfusion experiments, using 0.5 to 1.0 per 1000 concentrations. Disselhorst (1888) observed that irrigation of the frog mesentery with 0.05 per cent solution in normal saline produces progressive dilatation of the veins, but has practically no effect on the arteries. As early as 1881 Kirchner found that large doses of quinine produce a vasodilatation of the cerebral blood vessels and he observed in 3 out of 10 experiments hemorrhage in the floor of the fourth ventricle. Hirschfelder (1915) reported that quinine constricts the cerebral and retinal blood vessels in cats and rabbits, which corresponds to the findings of Biberfeld (1916); but Berezin (1916) observed vasodilatation in both rabbits and pikes. Similar contradictory reports were made by Niederehe (1918), who noticed a moderate constriction of the ear vessels of the rabbit; by Biberfeld (1916), who reported vasoconstriction of the peripheral vessels of the frog, and by Seto (1927), who observed a dilatation of both the ear vessels of the rabbit and the abdominal vein of the frog. According to Kosakae (1928) quinine dilates the blood vessels of the placenta. Akamatsu (1931) found that the vascular effect of quinine varies

with different organs and that in certain concentrations it inhibits the vasoconstriction by epinephrine nearly completely. This phenomenon may be easily observed in the frog, seldom in the rabbit ear and never in internal organs.

MacCarrison and Cornwall (1919) cautioned against the intravenous administration of quinine on account of the fall of blood pressure which may result. After intravenous injections of small quantities of quinine into rabbits Nelson (1927) observed a fall of blood pressure which he believed to be due to peripheral vasodilatation produced partly by depression of the vasomotor endings, partly by a direct action on the muscle. Niederehe (1918), however, found that the fall of blood pressure occurred only with larger doses (0.05 gram per kilogram rabbit) and is followed by collapse, rapid reduction of the pulse rate and pulse amplitude.

Quinine-epinephrine antagonism. The antagonism between quinine and epinephrine has been observed with the circulatory system. MacCarrison and Cornwall (1919) reported that the fall of blood pressure observed after the intravenous injections of quinine can be antagonized, but only incompletely, by the subsequent administration of epinephrine. Clerc and Pezzi (1919/20) stated that irregularities of the heart commonly observed after pressor doses of epinephrine do not occur when quinine has been given first and that, in sufficiently large doses, this may prevent any pressor action by epinephrine. From a decrease of the kidney volume, Clerc and Pezzi concluded that quinine causes vasoconstriction in the organ, but Nelson (1928) pointed out that this is presumably a passive phenomenon, caused by the fall of blood pressure. The persistent hypotension observed by Clerc and Pezzi in animals under quinine after the administration of epinephrine may be due to a persistent peripheral vasodilatation as assumed by Nelson (1927) or it may be caused by faulty technic as suggested by Hammet (1927). The effect of quinine on the vagus center seems to play a minor rôle, although Clerc and Deschamps (1923) assumed that quinine diminishes the contractility of the myocardium, affects the conductivity and paralyzes the vagus center and in large doses also the nerve trunk. These authors believe that the antagonism between quinine and epinephrine is due to inhibition of the stimulating effect of the latter on the vagus center and that neither the pressor nor the vasomotor action are involved in this phenomenon. Arrillaga, Gugliemetti

and Waldorp (1921) had observed the same antagonism with quinidine without attempting to give an explanation of this phenomenon. Jackson, Friedlaender and Lawrence (1922) gave as an explanation failure of the peripheral vessels to respond to epinephrine by vasoconstriction. Nelson (1927) agreed with Jackson and assumed that after the administration of quinine the peripheral vessels have lost the faculty to respond to epinephrine by constriction, presumably because of depression of the sympathetic nerve endings. He concluded this from the fact that the pressor response to pituitary, which acts on the vascular muscle directly, was not affected. The same opinion was expressed by Nakano (1927) and by Stake (1929). Larger doses of quinine which depress the vagus endings may also prevent cardiac slowing as observed after pressor doses of epinephrine.

The effect of quinine on the blood has been studied in several directions. It has already been stated that quinine disappears rapidly from the circulation. Numerous investigations have been made on the distribution of quinine between serum and erythrocytes. Morgenroth (1918) had found that red blood cells fix quinine *in vitro* and assumed that the same holds true *in vivo*. He considered this fixation to play an important rôle in the antimalarial action of quinine. It is generally accepted [Hatcher and Weiss (1926), Acton and King (1921)] that the distribution between serum and cells is about uniform, or according to Gibbs (1928) perhaps a little in favor of the cells. Schilling and Boeker (1919) believed that there is some difference as to the storage of quinine by red blood cells in normal and quinine-habituated persons, this being less marked in the latter. The amount of quinine stored in the cells goes parallel with concentration of quinine and the number of erythrocytes; it is also influenced by the temperature (Akashi, 1923). Shaw (1928) and Fourment and Hermann (1930) regarded this as an adsorption phenomenon, but the "Haftdruck" (pressure of solution) being very small, the amount adsorbed decreases rapidly after the intravenous injection of quinine (Broeker, 1920). Giemsa (1927), however, suggested that the conditions *in vivo* may differ from observations made on the adsorption made in test tube experiments. Concerning the observation of Akashi (1923) that in the presence of carbon dioxide no storage takes place in the red blood cells, Weise (1928) showed that this holds true only for extreme concentrations. Dixon and Premankur (1927) found that concentrations

of quinine of 1 : 400 produce hemolysis of red blood cells; according to Weise (1928) this depends on the amount of quinine brought in contact with the single blood corpuscle, i.e., the ratio between quinine and the number of red blood cells. Nocht and Kikuth (1929) observed that small doses of quinine stimulate the amboceptor hemolysis in the organism as observed in dogs, cats and rabbits; they found cinchonine ineffective in this respect. Quinine increases also the hemolytic action of cobra venom and it is in this respect antagonized by cholesterol. Since the cholesterol level in several malaria patients was found to be very low, the hemolytic properties of quinine may become more prominent in such patients, thus producing the symptoms characteristic for black-water fever. Marx (1906) claimed that quinine solution produces a specific alteration of the blood pigment, but it was later shown by Lewin (1909) that this is identical with methemoglobin.

The effect of quinine on leucocytes and their distribution. As early as 1868 Binz reported leucopenia in young cats after the administration of large doses of quinine. This phenomenon was studied more closely by Roth (1913), who found that 3 phases may be distinguished. Shortly after the drug has been given, a primary leucocytosis is observed, presumably due to contraction of the spleen and other organs; from 1 to 2 hours later this is followed by leucopenia, especially reduction of the polynuclears; and finally a stage of secondary leucocytosis in which lymphocytes, but especially the polynuclear cells, are increased. This had been found in general by Wilkinson (1896) and was later confirmed by Johannessohn (1918). The latter claimed that all white blood cells participate in this phenomenon and assumed that these changes were not due to a destruction but rather to a change of distribution. Grossmann (1923) claimed that intravenous injections of 0.2 gram of quinine hydrochloride cause no change in the number of leucocytes in the peripheral circulation in normal persons; but in patients suffering from liver injury he observed leucopenia. This reduction in the white blood cells may be seen about 20 minutes after the administration of the drug; they return to the normal level within the following hour. From experiments in rabbits reported by Kura (1932) it appears that the spleen may also be involved in the change of the distribution of leucocytes produced by quinine.

Scharrenbroich (1867) had found that quinine in concentra-

tions of 1 : 4000 inhibits the activity of leucocytes of mammals and in concentrations of 1 : 3000 those of the frog. Appert (1877) had noted that quinine solutions reduce the motility of leucocytes and that higher concentrations affect the circulation and prevent their accumulation on the vascular walls of the frog mesentery, while a moderate slowing of the circulation enhances their emigration from the blood vessels. Similar results were reported by Disselhorst (1888) and Schuhmacher (1894). Hamburger and Hekma (1908) found that 0.05 per cent solutions of quinine depress phagocytic processes; 0.1 per cent were much more toxic, and therapeutic concentrations or even concentrations of 0.001 per cent produced a depression of the phagocytic processes after 17 hours. Similar results were reported by Manwaring and Ruh (1907), namely, stimulation in concentrations of 0.005 per cent and inhibition in 0.025 per cent solutions. These phenomena may be explained perhaps by the observations of Maurel (1903), that 0.25 gram quinine added to a 100 cc. of rabbit blood produces a spheric shape of the leucocytes and kills them within 2 hours; and even smaller concentrations, as low as 0.005 per cent, produce this effect. From this it appears that we are dealing with a surface-tension phenomenon. This would also explain the observation of Ikeda (1916) already reported by Appert that quinine solutions inhibit the emigration of leucocytes into the surrounding tissue; and also that of Hirschhorn and Mulinos (1930) that quinine bisulfate solutions given to rabbits intravenously inhibit the inflammation produced by mustard oil on the cornea. In this reaction the margin of safety is very small, because the effective dose is very close to the minimal fatal dose. Favorable results were also reported by Susuki (1931), who studied the effect of quinine on the inflammation of the rabbit eye caused by injection of streptococcus suspensions.

The effect of quinine on the nervous system. The effect of therapeutic doses of quinine on the nervous system is not very marked. Bush (1920) observed stimulation of the cardio-inhibitory center by perfusing the turtle medulla with quinine solution. Sugata and Tatum (1923) assumed that it increases the irritability of the respiratory center. Nelson (1927) believed that failure of epinephrine to produce slowing of the heart after quinine is largely due to paralysis of the vagus mechanism, primarily of the peripheral nerve. The depressant effect of quinine on nerve fibers was already noted by Heubach (1876).

He found that when it is brought in contact with the nerve fiber it produces first a stimulation followed by progressive depression. This effect has suggested its use as local anesthetic and Schepelmann (1911) and Herzig (1914) believed that it may be quite useful in this respect, especially when proper solutions are used; its usefulness seems to be limited on account of the more or less marked irritation which it may produce. Dixon and Premankur (1927) assumed that this local anesthetic effect does not concern the nerve fibers as much as the nerve endings. But Cooper (1924) found that it affects the sciatic nerve of the frog in a way very similar to that of narcotics and that it gradually may kill the nerve.

The antipyretic action of quinine. The older literature on this subject has been extensively discussed by Rohde (1920). It was generally assumed that the antipyretic action of quinine is due to its depressant effect on the nitrogen metabolism (decreased heat production) and only secondarily to its vasomotor action (increased heat dissipation). Gottlieb (1890) had assumed a predominant effect on the metabolism, while that of the coal-tar antipyretics was said to be in the first line if not entirely of central origin. Calculated on the basis of the molecular weight, he used from 10 to 20 times larger doses of antipyrine, and therefore these experiments cannot be considered as conclusive. Stuehlinger (1899) observed reduction of the heat production in guinea pigs but not in rabbits. Feri (1911) found quinine effective in coli fever of rabbits but not in fever caused by tetrahydro-β-naphtholamine. After elimination of the central heat-regulating mechanism, Isenschmid (1913) found that quinine usually reduces the temperature. However, it seems to be questionable how far these results obtained under rather unphysiologic conditions may be transferred to normal conditions. After intracerebral injections in the neighborhood of the mid ventral portion of the caudate-nucleus Barbour and Wing (1930) reported a marked decrease of temperature and attributed this in part to the effect on the temperature centers. Hardikar (1925) pointed out that most of the previous work was made with intravenous or subcutaneous injections of the drug, and that in man with oral administration the heat dissipation seems to be the more important factor. The difference may be explained on the basis of different rates of absorption and also by differences of the susceptibility of the heat-regulating mechanism. He found that in normal and coli-

fever rabbits the subcutaneous administration of from 15 to 20 mg. per kilogram of quinine produces very little change in the respiratory exchange, but higher doses of up to 60 mg. cause a definite fall of the respiratory exchange and heat production, with simultaneous but moderate heat loss, this effect being only of short duration. In human subjects doses of up to 2 grams by mouth generally cause increased lung ventilation, respiratory exchange and heat production, with a greater increase of heat loss. He therefore believed that quinine acts on the central mechanism rather than on the peripheral tissues. Rosenthal and Lipschitz (1926) also came to the conclusion that the central heat-dissipating mechanism of the quinine antipyresis is more important than the metabolic effect. On the basis of basal metabolism studies Virchow (1927) believed that quinine acts by increasing the heat dissipation and that there is no difference between quinine and coal-tar antipyretics as to the mechanism of their action. Girndt (1929) also reached the conclusion that quinine antipyresis is of central origin. Finally Hiramatsu (1931) pointed out that the dose of quinine affecting the metabolism is much larger than the antipyretic dose. It appears, therefore, that the effect on the metabolism is the less important factor in the quinine antipyresis. Akamatsu (1931) assumed that the antipyretic action of small doses of quinine is of central origin, whereas large doses act by affecting the liver metabolism.

The effect of quinine on cardiac, smooth, uterine and striated muscle. Santesson (1892) found the frog heart weakened and its action slowed by quinine concentrations of 1 : 50,000; solutions 10 times more concentrated produce paralysis of the muscle. He also found the slowing to be due to lengthening of the refractory period, which has been confirmed by many investigators for both the mammalian and the amphibian heart. Burridge (1928) showed that quinine may also produce augmentative effects when higher dilutions (1 : 1,000,000) are used.

The action of quinine on the *intestinal* muscle was studied by Niederehe (1918), who found that it produces decrease of tone and amplitude. Dixon and Premankur (1927) claimed that it causes the longitudinal and the circular muscles of the intestine to contract synchronously, thereby reducing the tone but increasing the height of the contractions. Frey (1928) reported that concentrations of from 1 : 100,000 to 1 : 50,000 stimulate the longitudinal and the circular muscles of the tench; a more diluted

solution affects the interior smooth muscle layer more and diffuses gradually into the striated outer layer, whereas higher concentrations were found to affect mainly the outer striated circular layer. When used systemically, however, it seems to stimulate the intestine and for this reason its use has been suggested by Singer (1927) in postoperative intestinal depression and by Graham (1929) in chronic constipation.

Other smooth muscles such as the *tracheal* muscle may be relaxed (Trendelenburg, 1912), but Jackson (1913) observed bronchoconstriction which he believed to be due to muscular action. On the smooth muscle of the pigeon crop, Hanzlik and Butt (1928) observed only very doubtful or no action after the administration of 20 mg. quinine per kilogram. According to Biberfeld (1916) the constrictor muscle of the iris is stimulated by quinine, causing miosis. Waddell (1917) reported stimulation of the quiescent and active *vas deferens* of the guinea pig, rat, cat, and rabbit.

The effect of quinine on the *uterine* muscle has been evidently first observed by Monteverdi (1872); more recent clinical investigations were published by Baecker (1905), Kurdinowski (1906), Conitzer (1907), Maurer (1907) and others; it seems to be effective only after the beginning of labor, mainly reinforcing the uterine contractions, while it seems to be unable to induce labor in the quiescent uterus (Seggelke, 1921; Chopra, Dikshit and David, 1927). Kehrer (1907) working with the isolated rabbit uterus found that concentrations from 1.5 : 100,000 to 2.5 : 100,000 had a decidedly stimulating effect, whereas higher concentrations produced depression. Zanda (1910) claimed that quinine, cinchonine and cinchonidine increase the activity of the gravid dog uterus ante partum but not that of the empty uterus. He also observed that a well contracting uterus is stimulated but when functionating insufficiently it may be depressed by the same dose. On the isolated organ Niederehe (1918) observed depression with concentrations of 1 : 50,000. Stake (1929) reported similar results and noted that the poisoned uterus may become irresponsive to barium chloride. With concentrations of from 0.005 to 0.01 per cent of quinine Murakami (1930) observed a stimulating action on the rabbit uterus, the Fallopian tubes, the round ligaments and the vagina of the rabbit. Schuebel (1931) assumed that for obstetrical purposes 1 to 2 mg. quinine hydrochloride per kilogram should be sufficient to cause labor, that

smaller doses may sensitize the uterus for days to mechanical and chemical stimuli especially to the action of pituitary preparations. He also pointed out that large doses may cause depression of the uterus, also antagonizing the action of pituitary. Dodek (1932) came to the conclusion that the action of quinine on the uterine activity is unreliable in labor and in late pregnancy, although in some cases it may have a stimulant effect.

There exists also an antagonism between quinine and epinephrine in regard to their effect on the uterus. Chistoni (1922) showed that, in the pregnant rabbit uterus, quinine, in concentrations of 1:5000, abolishes the inhibitory effect of epinephrine and also the stimulatory effect of barium chloride. Langecker (1926) found that quinine hydrochloride in concentrations of from 1:30,000 to 1:100,000 prevents the effect of epinephrine. Stake (1929) assumed that massive doses of quinine paralyze the uterine muscle, moderate doses only the motor sympathetic nerve endings, while the inhibitory innervation is not affected. The same opinion was expressed by Murakami (1930).

Nelson (1928) investigated whether the antagonism between quinine and epinephrine existed also in other organs with sympathetic innervation. It seems to be restricted to the vasomotor and the uterine action because it was absent in the cervical sympathetic (dilator iridis), the orbital muscle of cat and dog, and in the chorda secretion of the dog. It was also found that the hyperglycemic action of epinephrine was not affected by the previous administration of quinine.

As early as 1797 Humboldt reported that cinchona extracts improve the excitability of frog *muscle* which had been rendered insusceptible to electric stimuli by repeated stimulation. In his extensive studies on the effect of quinine on striated muscle Santesson (1892) observed an increase in the energy of the frog gastrocnemius but also a greater tendency to fatigue. Von Fuerth and Schwarz (1909) reported increased energy by direct stimulation of the contractile substance of the muscle of the cat. Zipf (1929) pointed out that the action of quinine on the muscle depends to a considerable degree on the pH of the solution. He found that at pH 5.6 concentrations of 1:1000 to 1:3200 mol are required to produce the characteristic muscle action, whereas at pH 7.9 one-half this concentration, i.e., 1:6400 mol is sufficient, so that the free base is more effective than the salt. Riesser (1923) studied more closely the permanent contracture or the

rigor of the muscle produced by quinine. He compared the lactacidogen and the phosphoric acid content of the normal and of the quinine-poisoned muscle and found that in quinine solutions of 1 : 1000 the lactacidogen content of the muscle is rapidly reduced. In smaller concentrations (1 : 10,000) the same phenomenon occurs with the stimulated muscle, the free base being more effective than the salt. The decrease of lactic acid is paralleled by an increase of phosphoric acid, which he considered a symptom of increased permeability of the muscular membrane. Zipf (1929) has pointed out that this assumption is unnecessary because an increased formation of phosphoric acid would give the same phenomenon. Martino and Carbonaro (1926) reported similar observations, showing that under the influence of quinine the phosphagen content of the striated muscle was decreased and the inorganic phosphoric acid increased.

Irritant action of quinine. Subcutaneous administration of quinine may lead to more or less marked irritation and destruction of tissue as noted by Rhode (1921), Dudgeon (1919), Lange (1919) and others. This may be explained partly by the observations of Kleine (1901) that after subcutaneous injection a portion of the salt is precipitated as free alkaloid at the site of the injection, where it may remain for weeks. According to Klotz (1920) such accidents may be avoided by giving only small quantities in diluted solutions with the addition of gelatin. Secher (1915) found that concentrated solutions of quinine destroy the muscle tissue. Hildebrandt (1908) observed extensive hemorrhages of the stomach and the upper small intestine in rabbits after repeated oral administration of about 0.5 gram quinine per kilogram.

Toxic reactions of quinine. These may be classified as toxic reactions due to overdosage and as toxic phenomena resulting from hypersensitivity to the drug. Von Boeck and Bauer (1874) had already observed that administration of 1 gram quinine hydrochloride to a 4.5 kilogram dog produces rapid onset of convulsions followed by paralysis. Niederehe (1918) found that in rabbits death occurred by paralysis of the respiratory center. Macht (1928) reports that in various animals (rabbits, cats, and dogs) toxic doses produce tremor, spasmodic movements and stimulation of the respiration followed by paralysis. Macht and Teagarden (1923) had observed previously that the toxicity is greater in animals exposed to light than in those which are kept in the

dark. The effect of toxic doses on the circulation consists in a rapid fall of the blood pressure, ending in collapse. Weiss and Hatcher (1927) showed that with intravenous injections the toxicity depends largely upon the rate at which the drug enters the circulation and upon the inability of the liver to destroy the greater part of the drug administered. A. Hoffmann (1877) already suggested an injurious effect of quinine on the kidney manifested by the inability to excrete hippuric acid after the administration of glycine and benzoic acid. Cornwall (1919) found that continuous administration of quinine to rabbits for from six to eight months causes injury of the cellular elements of the kidney and of the adrenals, as well as some evidence of increased degeneration of the red blood cells in the spleen. Valenti (1914) also found sclerotic changes in the spleen and in the bone marrow after daily administration of 0.006 gram quinine per kilogram over a long period of time. The toxicity of quinine, therefore, is not at all a negligible factor and fatal poisoning may occur, especially since quinine is a favored constituent of patent medicines. Husemann (1888) reported 5 cases; Willimott (1931) reported 2 cases of severe poisoning, one of which was fatal; he also gives the more recent literature on this subject.

Already Runge (1880) had pointed out that after the obstetrical use of quinine the incidence of meconium is greater and that the weight of the infants is smaller than normally, which he considered as a toxic effect of quinine. More recently Dilling and Gemmell (1929) studied the effect on the fetus of quinine administered to mothers shortly *ante partum* to reinforce labor. They found 1.04 per cent of unaccountable cases of stillbirth among 765 cases. They recovered as much as 0.015 per cent of quinine from the urine of fetuses born from six to twelve hours after the administration of the drug to the mother, and 0.006 per cent in the *liquor amnii* under similar conditions. Sadler, Dilling and Gemmell (1930) found the concentration of quinine in still-born fetuses after the administration of therapeutic doses to the mother to range from 1: 50,000 to 1: 100,000, which they believed capable of producing toxic effects, as indicated by the greater frequency of the presence of meconium in the *liquor amnii.* One of the toxic symptoms of quinine concerns the eyesight and the auditory organs, which are usually designated as cinchonism. After oral administration of 1 gram of quinine to rabbits Kirchner (1881) observed hyperemia and ecchymoses

in the mucosa of the cavum tympani. The auditory disturbances were studied in detail by Wittmaak (1903), who also cited the literature on this subject; he reached the conclusion that the auditory disturbances, ringing in the ears and deafness, are functional disturbances due to changes of the ganglion spirale and that circulatory disturbances have only minor or no direct effect, although they may be the cause of the pathological changes of the nerve cells. Recently Okonogi (1930) studied the acoustic disturbances produced by quinine after repeated subcutaneous injections in animals and found no change in the organ of Corti, but occasionally the ganglionic cells of the cochlea and of the vestibulum showed dissolution of the Nissl bodies, chromatolysis and displacement of the nuclei, indicating a possible degeneration of the ganglion cells. The visual disturbances, temporary or permanent amblyopia, as reported by von Speyer (1914) and others are due, according to Harnack (1912), to spastic vasoconstriction which, if of sufficient duration, may cause secondary degeneration of the nervous tissue. The same explanation was given by Shahan (1916). Renescu and Dorogan (1932) described the rather complicated changes of the histological structure of the sciatic of the frog under the influence of quinine.

Probably the first authentic description of quinine idiosyncrasy is that of J. Burney Yeo (1889), who observed local rashes on the lower extremities. After the attention had been directed towards such effects, numerous observations were reported (Samaja, 1918; Van der Horst, 1918; Larreglo, 1930). Stelwagon (1901) reported cases which were not only susceptible to the oral administration of the drug but who showed also the same reaction after contact of the skin with quinine preparations such as hair tonics and mouth washes. Moreschi (1920) showed that quinine idiosyncrasy can be acquired and it has been suggested that black-water fever is also a symptom of acquired quinine idiosyncrasy. Recently Dawson and Garbade (1930) found that idiosyncrasy against quinine may extend to cinchonine and levorotatory cupreine derivatives, such as ethyl hydrocupreine, but not necessarily to their dextrorotatory isomers such as quinidine, optoquinidine and cinchonidine. Dawson and Newman (1931) and Sanders (1931) reported cases of quinine idiosyncrasy which were successfully treated with quinidine.

The effect of quinine on the fermentative action, on proteins and on cells may be explained in part by its tendency to con-

centrate on the surface. Its toxicity is markedly influenced by different electrolytes, as indicated by the work of J. Brailsford Robertson (1905/06), and Kehar (1930).

By addition of halogenalkyl or alkylhydrate on the nitrogen of the quinoline or of the piperidine ring, quaternary bases such as methyl and diethyl quinine are formed with curare-like action (Santesson, 1895).

Quinidine.

Quinidine (*conchinine*) is the dextrorotatory isomer of quinine. According to Giemsa and Werner (1914), it is at least equal to quinine in regard to its *antimalarial action;* in cases of quinine idiosyncrasy it may, therefore, be a valuable substitute. This recently was confirmed by Dawson and Garbade (1930), who showed that idiosyncrasy against levorotatory quinine alkaloids may not extend to dextrorotatory isomers. In Nagana infections of white mice, Cohn (1913) found it equally as effective as quinine; the latter seemed to be superior only in oily solutions and in the treatment of relapses. According to Rona and Bloch (1920) the inhibitory effect of quinidine on the invertase action is more marked than that of quinine. Piccinini (1926) found that it is less effective in inhibiting amylotic processes, which was confirmed by Ohlson (1930). Samura (1930) found that like other cinchona alkaloids it inhibits the growth of fibroblasts in cultures, the inhibition being parallel to the concentration of the drug. Irregular, polygonal rounded forms were noted in the zone of growth and the cytoplasm contained fat droplets and vacuoles.

Wiechmann (1918) found that quinidine is largely excreted undecomposed in the urine, the *excretion* being greater after fractional doses than after single doses, the more soluble salts being more quickly absorbed and more rapidly excreted. Patients suffering from auricular fibrillation are said to excrete less than normal persons. According to Weiss and Hatcher (1927) 95 per cent of the dose given intravenously leaves the blood within five minutes; after 1 hour 1 per cent may still be excreted and from 3 to 4 hours later only traces can be detected in the circulation. The rate of disappearance seems to vary with different individuals. After its absorption quinidine is loosely fixed in the organs and is easily removed by perfusion. The concentration in different organs changes with the time. First the lungs are said

to contain the largest quantity, later kidney and liver are richer, the latter destroying quinidine at the same rate as quinine. The excretion is practically completed after 3 to 4 hours.

Its *antipyretic efficiency* as tested by Struempel (1878) in various infectious diseases is the same as that of quinine, and it has comparatively little side action.

The *effect of quinidine on the heart* was first studied by Santesson (1892), who found that it reduces the heart rate and the volume of the pulse more constantly than quinine and that it affects the frequency more than the volume. He found its action as a whole weaker than that of quinine and it seems to affect the motor ganglia more than the ventricular muscle. Fredericq (1913) found it less toxic than quinine for the turtle heart; the manner of action was similar, though arrhythmic periods may be more frequent. Clerc and Deschamps (1923) found it more effective in the isolated dog heart, but otherwise very similar to quinine. Waddell and Cohn (1920) believed that it affects the auricle and ventricle in the same manner, the effect on the latter being more marked. With small doses the rate is slowed; larger doses produce diastolic arrest. Quinidine decreases the diastolic tone and the irritability, but even if the heart is completely inhibited it may respond to mechanical and electrical stimulation. Quinidine decreases also the elasticity and lengthens the refractory period. In experiments with the turtle heart, Love (1926) found that the absolute refractory period, i.e., the interval between the last rhythmic stimulation and the earliest test shock which delays or abolishes the response to a second test shock, is actually shortened under the influence of quinidine. But according to Lewis and Drury (1926) it lengthens the effective refractory period on which effect its therapeutic action in cardiac fibrillation is based. Since it decreases the conduction, it lengthens the auricular-ventricular (A-V) interval, finally producing A-V block. Atropine does not alter the reaction, epinephrine is still effective. Dale (1922) considers the quinidine action in part as an effect on the vagus mechanism but in a different manner than that produced by atropine, because neither the peripheral vagus endings nor the responsiveness of the cardiac muscle seem to be affected by quinidine. Bodo (1928) found that quinidine produces dilatation of the ventricles independent of the dilatation produced from the prolonged inflow and that in larger doses it diminishes the coronary flow. Jackson, Fried-

laender and Lawrence (1922) also assume that it does not affect the vagus endings, but that, on the contrary, it renders the heart more susceptible to vagus stimulation. The similarity of its action to that of nicotine and curare may indicate that it acts on the autonomic cells, stationed on the path of the vagus. Haskel (1928), who studied the effect of quinidine on hearts poisoned by digitalis, believed that the curative action of quinidine is due more to the vagus action than to the direct muscular action.

Wenkebach (1918) was the first to use quinidine to restore the normal rhythm in cardiac fibrillation. F. B. Hoffmann (1920) found that in isolated dog and cat hearts quinidine reduces the vigor of the auricular contractions considerably, the frequency less and the irritability very distinctly, so that it is impossible to produce auricular fibrillation. Lewis, Drury, Iliescu and Wedd (1921) found that it lengthens the refractory period, that it delays the recovery of the muscle and that it slows the conductivity. Arrillaga, Gugliemetti and Waldorp (1921) also assumed that the therapeutic effect of quinidine is probably due to the reduction of the excitability and lengthening of the refractory period. By lengthening the refractory period quinidine tends to slow the gap, and by its effect on the conduction it tends to lengthen it. For this reason circus movements will stop only in cases in which the first action takes place. Lewis (1922) pointed out that the usefulness of the drug in auricular fibrillation is restricted to the earlier cases, while other cases and patients with venous stasis do not respond as readily. Similar indications were later given by Parkinson and Campbell (1929), who stated that, in serious cardiac failure and marked dilatation of the ventricle, quinidine is less indicated than is digitalis. Newman (1928) thought its use to be indicated only when the ventricle is beating vigorously; with poor ventricular functionation it may do more harm than good, since it depresses both the auricle and the ventricle. Quinidine, like quinine, does not improve the cardiac action when the cardiac muscle is in a poor nutritional condition. De Boer (1922) and Gold, Modell and Price (1932) caution against its use in the presence of auricular-ventricular block. Harris (1929) gave statistics on the curative value of quinidine in auricular fibrillation. These show that the drug is effective in 60.5 per cent of the cases and that the beneficial results may last for months and occasionally for years. Okamoto (1930) also believed that quinidine is superior to quinine in auricular

fibrillation, and that acetylquinidine is more effective than quinidine. As regards the blood pressure quinidine seems to be more apt to produce a fall than quinine and the recovery is said to be less prompt and less complete (Nelson, 1927). It antagonizes the vascular effect of epinephrine in the same way as quinine (Arrillaga, Gugliemetti and Waldorp, 1921; Jackson, Friedlaender and Lawrence, 1922). According to Stake (1929) the vasodilator action is less marked than that of quinine. The hemolytic properties are the same for quinine and quinidine, according to Cohn (1913).

On *striated muscle* the effect of quinidine is less marked than that of quinine (Santesson, 1892). According to Brody (1927) the depression is more marked and also the lengthening of the refractory period is more distinct with quinidine than with quinine. This is not in accordance with the results reported by Veley and Waller (1909), who found quinidine about one-half as toxic as quinine for striated muscle. The uterine action was found by Hale (1915) to be 10 times more effective than that of quinine in the isolated uterus and in the living cat. According to Nelson (1927) the stimulating concentration for the uterus is from 1:85,000 to 1:60,000, higher concentrations being depressant. He seldom observed marked persistent increase of the tone in the isolated uterus and never *in situ*. In the isolated organ it seemed to be slightly more effective than quinine, but *in situ* he found little difference. The response of the uterus to the drug may, however, vary considerably, depending upon its condition. Chopra, Dikshit and David (1928) found that the intravenous injection of 5 mg. of quinidine produced in virgin cat uteri well marked relaxation, preceded sometimes by primary contractions; neither effect is observed regularly in pregnant and multiparous animals, and pregnant uteri show a well marked contraction which is not tonic. They found no evidence that quinidine is a stronger oxytocic agent than quinine. Zanda (1910) claimed that quinidine causes only a post partum contracture in the uterus of dogs, while quinine, cinchonine and cinchonidine increase also the contractility of the gravid uterus ante partum.

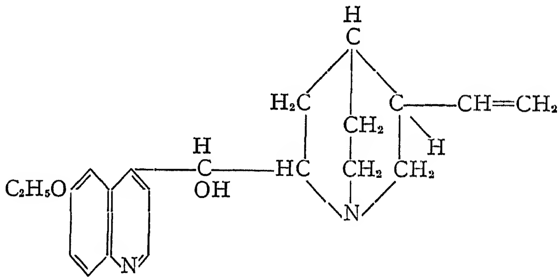
As to the *toxicity* of quinidine Nelson (1927) believed that it is slightly but definitely more toxic than quinine as determined in rats by intraperitoneal injection and in frogs by injection into the lymph sac. Niccolini (1928) reported one fatal case of quini-

dine poisoning after a total dose of 10 grams and claimed that it is more toxic than quinine.

In comparing the pharmacologic action of the dextro- and levorotatory compounds, quinine and quinidine, it appears that there is very little difference between the two which would warrant definite conclusions as to the effect produced by the different position of the hydroxy radicle in the secondary alcohol group. If there is any difference, this may be in their cardiac action, the effect of quinidine being more marked on the refractory period and less marked as to the muscular depression. The toxicity of quinidine seems also to be slightly greater than that of quinine.

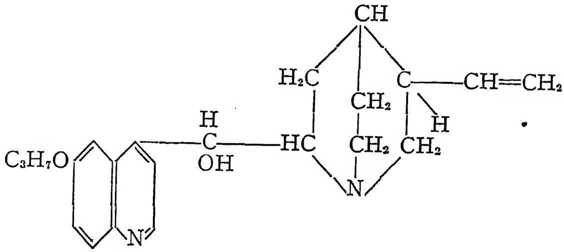
Alkylcupreines.

Grimaux and Arnaud (1891) prepared the higher homologs of quinine, **ethyl, propyl and allyl cupreine.** The *ethyl* compound represents a white amorphous powder. The hydrate melts at 60° C., the dry substance at 160° C. It is very soluble in alcohol ether and chloroform; the aqueous solution when acidulated with sulfuric acid shows very marked fluorescence. **Ethylcupreine**



is levorotatory and produces the same side actions as quinine (*ivresse quininique*), it has distinct local anesthetic properties, and it is also effective as an antipyretic. Since it is more toxic than quinine and cupreine, it has not been used extensively although it has marked antimalarial properties. This was confirmed by Baermann (1914) and by Giemsa and Werner (1914), but the latter found that the higher homologs show a distinct decrease of the antimalarial action, so that *two carbons in the quinoline side chain appear to be the optimum in this respect.*

Grimaux, Laborde and Bourru (**1894**) also studied the higher homolog, **propyl cupreine,**



The free base is a white powder, the anhydrous preparation melting at 164° C. Given subcutaneously to rabbits, 25 mg. produce a marked fall of the temperature of up to 5° C., and tremor, incoordination and depression, from which the animal may recover. The drug has also a marked local anesthetic effect which outlasts the depressant stage. The substance is 4 times as toxic as quinine; producing severe side actions, such as ringing of the ears, vertigo and nausea. The antimalarial properties according to Giemsa and Werner (**1914**) are less marked than those of ethylcupreine.

Comparison of the pharmacologic action of quinine with that of cinchonine reveals the following differences:

The bitter taste characteristic for quinine is less marked in cinchonine. The antimalarial action is present in cinchonine, but is less marked than with quinine. The effect on the cardiac muscle seems to be about the same with both compounds, cinchonine having evidently more effect on the nervous regulator mechanism. The depressant effect on the muscle seems, according to Santesson, and to Veley and Waller, to be about the same, and the toxic effect on the vagus center. (Clerc and Pezzi) seems to be less marked than with quinine. The observation of Ikeda that cinchonine does not affect the emigration of leucocytes as quinine does, may lead to an explanation of these differences. Unfortunately Maurel did not extend to cinchonine his investigations on the effect of quinine on the form changes of leucocytes; this and comparative measurements of the surface tension phenomenon may throw some light on the differences in their pharmacologic action.

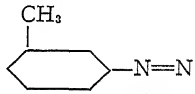
Comparison of the pharmacologic action of quinine and cu-

preine: In cupreine the antimalarial action is not materially improved above that of cinchonine, being distinctly inferior to that of quinine. The toxicity of cupreine is half that of quinine, indicating that the free hydroxy group may enhance the detoxication in the organism. The antipyretic action seems also to be less prompt than with quinine.

From these data it becomes evident that the methoxy group, although enhancing the antimalarial action, is not the essential factor in this action of quinine. This is in accordance with the findings of Shaw that the removal of the methoxy group has only a slight, although a distinct effect on the partition coefficient between the red blood cells and the solution containing the alkaloids.

Substitution in the Quinoline Ring.

This does not affect the antimalarial action of quinine, at least as far as such compounds have been studied. Giemsa, Weise and Tropp (1926) investigated a series of hydroquinine derivatives in which the 5-hydrogen atom in the quinoline ring was substituted by an amino group, by chlorine and by bromine. All these compounds showed the same antimalarial properties as hydroquinine. Shaw (1928) studied the partition coefficient between red blood cells and the solutions of such compounds. He found that the introduction of azo dyes such as



in the 5- position resulted in a marked increase of the partition coefficient, whereas the introduction of azo groups containing ionic groups yielding ions at a pH of 7.4 reduces the coefficient markedly as, for instance, in phenylarsonic acid azohydrocupreine. Boyd (1926) studied, in malaria of birds, some azo derivatives of this type which were prepared by Heidelberger and Jacobs (1919/20) namely, **p-methoxyphenylazohydrocupreine, m-tolylazohydrocupreine, o-ethoxy-phenylazohydrocupreine, 5-aminohydroquinine, 5-amino-8-phenylazohydroquinine, and 5-hydroxy-8-phenylazohydroquinine.** The first two of these were found to be extremely toxic for birds, but only the m-tolylazohydrocupreine hydrochloride was able to kill *Plasmodium praecox in vitro* but it had only a moderate effect *in vivo*. It had, also, a marked hemolytic action which is less marked with 5-aminohydroquinine.

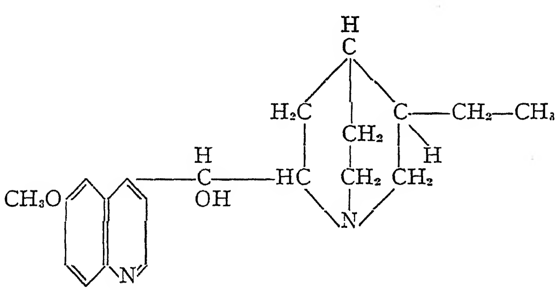
One of the characteristic groups of quinine is the *vinyl group*, $>\underset{H}{C}-\underset{H}{C}=CH_2$. Shifting of the double bond closer to the piperidine ring $>C=\underset{H}{C}-CH_3$ yields an isomer, called *isoquinine.* It has a bitter taste like quinine, forms fine needles melting at 185° C., and is soluble in organic solvents. According to Bachem (**1910**) this compound is more toxic for paramecia than is quinine, while the toxicity for higher animals is the same.

Therefore the position of the double bond in the side chain seems to be of no great importance.

Changes of the Vinyl Group.

Changing the double bond of the vinyl group into a triple bond, $>\underset{H}{C}-C\equiv CH$, yields *dehydroquinine.* Schroeder (**1913**) found that it is half as toxic as quinine for paramecia, also less bacteriostatic; and that its antipyretic action is the same as that of quinine. Giemsa, Weise and Tropp (**1926**) stated that it is very toxic but that it has only moderate antimalarial properties. This difference may be explained by the greater instability of the triple bond.

Reduction of the vinyl group of cupreine with the formation of an ethyl group yields hydrocupreine; that of quinine **hydroquine.** The latter crystallizes with two molecules of water. The



water-free preparation melts at 172° C., is soluble in most organic solvents and is levorotatory like quinine. Reid Hunt (**1903**) determined the minimal fatal dose for mice to be 0.33 mg. per gram body weight as compared with 0.37 mg. of quinine, this compound being therefore slightly more toxic. This was confirmed for birds by Boyd (**1926**), who determined the minimal fatal dose of quinine as 4 mg.; that of hydroquinine as 2.5 mg. For paramecia the toxicity of hydroquinine seems to be slightly

reduced. Morgenroth and Halberstaedter (**1911**) found it to be more effective in trypanosome infections than quinine. According to Giemsa and Werner (**1914**) its antimalarial properties are also more marked than those of quinine. This was confirmed by Baermann (**1914**).

Morgenroth and Ginsberg (**1913**) estimated its local anesthetic action to be from 2.5 to 3 times stronger than that of quinine.

Giemsa, Weise and Tropp (**1926**) and Giemsa and Werner (**1914**) compared the antimalarial action of quinine, cupreine, ethylcupreine and cinchonine with the corresponding hydrocompounds. They found that in the case of quinine and cupreine the antimalarial action was increased by the reduction of the vinyl group, while cinchonine which has hardly any antimalarial properties, was not improved. Goodson, Thomas and Macfie (**1930**) reported also that in bird malaria hydroquinine has more marked antimalarial activity than quinine. Borchardt (**1930**) found that hydroquinine is less toxic than quinine when brought in direct contact with *Plasmodium praecox* prior to the subsequent inoculation of birds. Boyd (**1926**) observed that hydroquinine and hexahydroquinine are only slightly more toxic than quinine for birds but that both have marked hemolytic properties.

Dihydrocupreine is identical with the natural alkaloid quinamine. Chopra and David (**1927**) found it not very toxic for bacteria and protozoa. It has little effect on the digestive enzymes and its action on the circulation is also less marked than with other cinchona alkaloids. It stimulates the peristaltic movements of the intestine and increases its tone as well as that of the uterus. Its local anesthetic properties, determined on the rabbit cornea and by blocking the nerve, are said to be as marked as those of cocaine. Chopra, Dikshit and David (**1928**) studied its effect on the uterus more closely. With intravenous injections of from 3 to 4 mg. they observed well marked tonic contractions in the virgin cat uterus, increase of tone and automatic movements of the non-pregnant multiparous uterus and marked increase of tone of the pregnant uterus. Concentrations of 1 : 300,000 were found to produce a distinct contraction of the isolated virgin uterus.

According to Giemsa, Werner and Tropp (**1914**) **hydroquinidine** did not show better antimalarial effects than quinidine and ethylhydrocupreine was less effective than ethylcupreine.

Dihydrocinchonine, also called **cinchonamine** as a natural alkaloid, is isolated from the bark of *Remija purdiana*. Accord-

ing to Sée and Bochefontaine (1885), when given subcutaneously to rabbits in doses of 0.25 gram, it produces short marked convulsions, killing the animal within from 3 to 4 minutes. In frogs 0.01 gram produces arrest of the heart within from 18 to 20 minutes. They considered it to be 6 times as toxic as quinine and cinchonine. This was confirmed by Veley and Waller (1909), who found it to be 4 times as toxic as quinine for striated muscle.

The observation of Dawson and Garbade (1930) that quinine-sensitive persons respond in the same way to the dihydro-compound seems to indicate that the reduction of the vinyl group does not materially alter the mechanism of the action of quinine.

Felton and Dougherty (1922) investigated a series of hydroquinine derivatives, in which the nitrogen of the nucleidine ring was changed to a quaternary base, as to their antiseptic value in the treatment of mice infected with pneumococci. The following compounds which had previously been synthesized by Jacobs and Heidelberger (1919) were used: **Hydroquinine-chloroacetamide, hydroquinine-chloroacetanilide, hydroquinine-p-chloroacetylaminophenol hydrochloride, hydroquinine-m-chloroacetylaminophenol, and hydroquinine-4-chloroacetylaminopyrocatechol hydrochloride.** They found that all these compounds have marked pneumococcicidal action both *in vitro* and *in vivo* with mice, being, however, less effective in rabbits. Their action was found to be quicker but less lasting than that of optoquine on account of the more rapid decomposition. The introduction of a hydroxy group into the benzene nucleus of hydroquininechloroacetanilide, with formation of the corresponding p-chloroamidophenol, shifts the relation between organotropism and bacteriotropism in the direction of the latter, the parahydroxy derivative being only one-fifth as toxic as the anilide and only one-tenth less active as a bactericidal agent. Shifting the hydroxy group from the para to the meta position renders the compound half as toxic while maintaining the same bactericidal activity. The pyrocatechol compound is one-eighth as toxic and one-fifth as bactericidal as the anilide.

Boyd (1926) reported on the toxicity, the hemolytic properties and the efficiency against *Plasmodium praecox* infections in birds for the following compounds of the same type, also prepared by Jacobs and Heidelberger (1920), namely: **Hydroquinine chloroacetdiethylamide, hydroquinine chloroacetylaminoguaiacol, and hydroquinine chloroacetyl-p-anisidine.** The first was

found to be only slightly toxic and the last two only little more so than quinine hydrochloride. The first two kill the plasmodia *in vivo* and *in vitro* and have only slight or no hemolytic properties.

Removal of the double bond by the addition of one molecule of hydrochloric acid may yield the **hydrochloroquinine** having the group $>\underset{H}{C}-\overset{H}{\underset{H}{C}}-\overset{Cl}{CH_2}$ in the side chain and the **hydrochloro-iso quinine** having the group $>\underset{H}{C}-\overset{Cl}{\underset{H}{C}}-\overset{H}{CH_2}$.

The minimal fatal dose of the former was determined as 0.81 mg. per gram of mouse, so that it is distinctly less toxic than quinine, while the toxicity for infusoria is distinctly greater (Reid Hunt, 1903). The toxicity of the iso compound was found by Bachem (1910) also to be smaller than that of quinine and its toxic action on paramecia also somewhat greater, so that there is evidently no great difference in the toxicity of the two compounds. Morgenroth and Halberstaedter (1910) found it more effective in trypanosome infections than quinine but without sufficient therapeutic value.

A bromine substituted quinine derivative containing the group $>\underset{H}{C}-\overset{H}{C}=\overset{Br}{\underset{H}{C}}$ and a **dibromquinine,** $>\underset{H}{C}-\overset{Br}{\underset{H}{C}}-\overset{Br}{\underset{H_2}{C}}$, were prepared by Christensen (1901/04). Schroeder (1922) found these compounds more toxic than quinine for paramecia, four to five times as bacteriostatic and more depressant for the frog heart. When injected subcutaneously they produced marked local irritation terminating in necrosis, being in this direction also much more toxic than quinine.

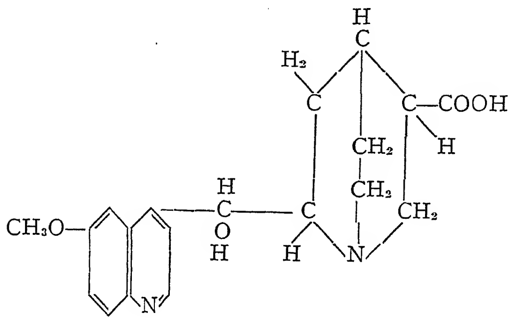
Giemsa, Weise and Tropp (1926) found **hydrochloroquinine, hydroiodoquinine** and **quinine dibromide** equal to quinine in antimalarial action.

Thus it appears that the double bond in the side chain and substitution of haloids does not interfere with the antimalarial action. The same holds true for aminohydroquinine.

The corresponding **hydroxyhydroquinine** was studied by Reid Hunt (1903) as to its toxicity for mice and paramecia and this was found to be lower than that of quinine.

Oxidation of the vinyl group of the quinine molecule by means

of potassium permanganate changes it to a carboxyl group yielding a substance called **quitenine,**



This compound, with a melting point of 285° C., is probably identical with the dihydroxyquinine of Kerner (**1870**). He found that this is less toxic than quinine for infusoria; that it does not interfere with the oxidase reaction and that it has neither antiseptic nor markedly toxic properties. This weak pharmacologic activity was confirmed by Dixon and Premankur (**1927**). Dauber (**1920**) showed, however, that some infusoria are quite sensitive to this compound. Hirschfelder, Jensen and Swanson (**1923**) found it one-third to one-fourth as toxic as quinine for rats, and that as to its antiseptic properties it is more toxic for gram positive bacilli than for gram negative. Giemsa, Weise and Tropp (**1926**) stated that it is ineffective against malaria of birds. Dauber (**1920**) reported that the depressant effect on the isolated frog heart is qualitatively that of quinine, but quantitatively much weaker. This was confirmed by Dixon and Premankur (**1927**). The circulation and respiration of rabbits are not affected by the subcutaneous administration of 0.1 gram. The hemolytic action is half as strong as that of quinine. It has very little effect on smooth and striated muscle and depresses the isolated uterus. It is largely excreted unchanged in the urine and does not affect the uric acid excretion. It is interesting, however, that in rabbits on a diet of oats with which the animals excrete acid urine, quitenine produces very marked changes of the kidney, characterized by the presence of casts, albumen and blood in the urine and by desquamation of the tubular apparatus (Dauber, **1920**). These changes do not occur, however, if the animal is kept on a diet which renders the urine alkaline.

It appears, therefore, that the oxidation of the vinyl group to a carboxyl group reduces the toxicity of quinine considerably. This changes also the physico-chemical properties of the compound, for Shaw (1928) found that the partition coefficient between red blood cells and quitenine solutions is very small.

The oxidation of the vinyl group in cinchonine yields **cinchotenine.** This compound and **hydrocinchotenine** as well as **quiniditine** are also considerably less toxic in every respect than cinchonine and quinidine (Dauber, 1920).

That oxidation of the vinyl group or the existence of a carboxyl group in its place interferes markedly with the typical quinine action is evident from the report of Dawson and Garbade (1930) that the "tenines" do not produce a reaction in persons sensitive to the mother alkaloids.

Masking the free carboxyl group by esterification, however, again renders quitenine more effective, which is paralleled by the reappearance of the anthelmintic action of santonicethylester as compared with the ineffective santonic acid. Giemsa, Weise and Tropp (1926) found that *ethylquitenine* is again quite effective in malaria of birds. Dawson and Garbade (1930) observed the reappearance of toxic reactions in quinine-sensitive persons, and Shaw (1928) found that the partition coefficient between red blood cells and the solution of the compound shows a considerable increase, but without reaching that of quinine.

It appears, therefore, that the vinyl group is not needed for the antimalarial action of quinine, and that its change to an ethyl group renders the new compound even more effective. Removal of the double bond by the addition of hydrochloric acid, ammonia and water does not affect the efficiency markedly. Transformation of the double bond into a triple bond reduces the efficiency, and oxidation of the vinyl group to a carboxyl group abolishes it completely. Although the efficiency of the latter compound (quitenine) can be restored in part by esterification, the new compound is less effective, presumably because the ester is saponified in the organism.

Effect of changes of the secondary alcoholic group on the pharmacologic action.

It has been shown that stereoisomeric changes in the secondary alcohol group, as in quinine and quinidine, cinchonine and cin-

chonidine do not produce very marked changes of the antimalarial action of these compounds nor do they affect the partition coefficient between red blood cells and their solutions.

Quininechloride with the group $\overset{\mathrm{H}}{\underset{\mathrm{Cl}}{-\mathrm{C}-}}$ has no antimalarial properties according to Giemsa, Weise and Tropp (**1926**). In nagana infections Cohn (**1913**) found its trypanocidal action and that of **ethylhydrocupreinechloride** still present, although reduced.

Oxidation of the alcoholic group yields the keto compound containing the group $\underset{\mathrm{O}}{\overset{-\mathrm{C}-}{\|}}$ (Rabe, **1908**). Such derivatives are **quininone** from quinine, **cinchonone** from cinchonine, and **hydrocinchonone** from hydrocinchonine. These compounds were studied by Cohn (**1913**) in nagana infected mice. Since the mother substances are not very effective against these infections the negative or positive outcome in using the ketones is not very convincing. Hildebrandt (**1908**) found that cinchonone resembles cinchonine closely in its pharmacologic properties. In rabbits 0.5 gram per kilogram given orally produces occasional convulsions from which the animals recover. After a few days, however, they die, and extensive hemorrhages are found in the stomach and the upper small intestine. Since cinchonine can be recovered from the urine after its administration it must be partly reconverted into cinchonine in the organism; most of it, however, is excreted in the form of conjugated glucuronic acid.

Reduction of the hydroxyl group with the formation of **desoxyquinine** (Koenigs, **1895/96**) containing the group $\overset{\mathrm{H}}{\underset{\mathrm{H}}{-\mathrm{C}-}}$ destroys the antimalarial properties completely (Giemsa, Weise and Tropp, **1926**). According to Fuchs (**1899**) it is more toxic than quinine for paramecia, frogs, mice, and guinea pigs. The increased toxicity of this compound is paralleled by that of **desoxyconchinine, desoxycinchonine** and **desoxycinchonidine** (Fuchs, **1899**).

It appears, therefore, that reduction of the alcoholic group increases the toxicity of quinine and antagonizes the antimalarial properties completely.

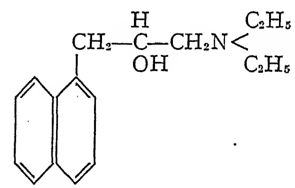
Heidelberger and Jacobs (**1920**) also prepared a **β-hexahydrocinchonane hydrochloride** which is only slightly more toxic for

birds than quinine, and which was found to be only slightly effective in bird malaria and only in single massive doses, repeated fractional doses being ineffective. Its hemolytic action is about the same as that of quinine (Boyd, 1926).

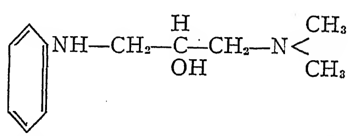
Quinene, which contains the group $\overset{H}{=C-}$ has no antimalarial properties according to Giemsa, Weise and Tropp (1926). The corresponding cinchonine derivative, **cinchonene**, increases the reflex excitability of the frog, even in small doses, and produces first tetanus and then paralysis, the heart continuing to beat. Dauber (1920) found it to be five times as toxic as quinine.

It appears, therefore, that the antimalarial properties of quinine are closely connected with the existence of the secondary alcohol group between the quinoline and the quinuclidine ring.

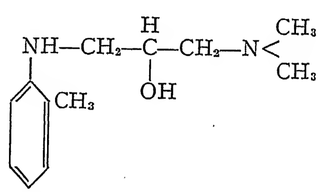
Starting from this assumption, Fourneau, Trefouel, Stefanopuolo, Benoit, De Lestrange and Melville (1930) synthesized a great number of secondary amino alcohols. From these the following showed some effect in avian malaria but were found ineffective in man:



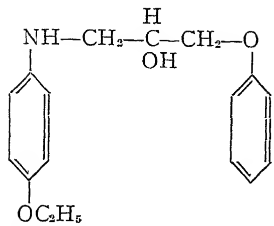
1-(α-naphthyl)-3-diethylaminopropanol-2



1-phenylamino-3-dimethylaminopropanol-2



1-(o-tolyl) amino-3-dimethylaminopropanol-2



1-(p-phenetyl) amino-3-phenoxypropanol-2

Therefore, it appears that the secondary alcohol group alone is not the carrier of the antimalarial action of quinine, but that we are dealing with the synergistic action of a number of different groups or factors.

Effect of changes of the quinuclidine ring on the pharmacologic action.

Changes of the quinuclidine or loipone ring can be produced by prolonged boiling of quinine with diluted acetic acid. The resulting compound is **quinotoxine**, which was discussed with the chemistry of the cinchona alkaloids. In this compound, an isomer of quinine, the loipone ring is changed to a piperidine ring with a side chain leading to the secondary alcohol group which is transformed into a keto group. According to Giemsa, Weise and Tropp (1926) quinotoxine has no antimalarial properties and Reid Hunt (1903) found it less toxic than quinine for infusoria and mice. This was confirmed by Biberfeld (1916). Hildebrandt (1916) on the contrary, believed it to be more toxic than quinine and markedly less toxic than cinchotoxine, which he attributed to the presence of the methoxy group. He observed with rabbits that small doses produce an increase of the blood pressure without affecting the heart rate; and that it is partly excreted as conjugated glucuronic acid. Biberfeld (1916) working on frogs found its effect on the circulation and on smooth muscle very similar to that of quinine and did not see the stimulating effect on the blood pressure described by Hildebrandt. He tested also the antipyretic and local anesthetic properties of this compound; while no antipyretic action could be discovered, quinotoxine showed a slight local anesthetic effect. Dawson and Garbade reported that both quinine-sensitive and normal persons respond to quinotoxine with irritation of the skin; when the solution was neutralized, however, there was no reaction. This irritant action of quinotoxine may explain the skin reactions observed in workers

with quinoidine residues. According to Shaw (**1928**) the partition coefficient between red blood cells and the solution of the compound is not altered by changing quinine to quinotoxine.

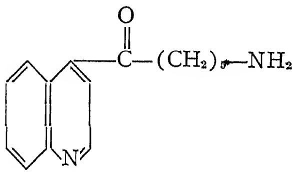
The name quinotoxine and the assumption of Kaufmann (**1913**) that quinine may be changed to quinotoxine in the organism, for a time gave rise to the fear of therapeutic quinotoxine poisoning. As Sollmann (**1921**) has pointed out, this fear is not warranted, because the toxicity of quinotoxine is hardly, if at all, greater than that of quinine and it can scarcely be formed in the organism. Even when quinine is prescribed with organic acids the danger from a toxic action due to the formation of quinotoxine would be out of the range of the probability. Bachstez and de Caro (**1932**) also believed that it is not very likely that the conversion of quinine to quinotoxine plays an important rôle in the toxic symptoms occasionally produced by quinine.

Hydroquinotoxine was studied in nagana infections by Cohn (**1913**), who found it more toxic and more effective than hydroquinine.

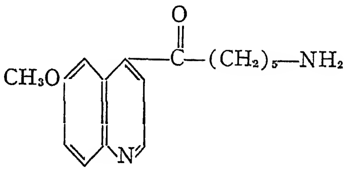
Cinchotoxine, the "toxine" corresponding to cinchonine, is highly toxic according to Hildebrandt (**1908**), the minimal fatal dose for mice, 0.15 mg. per gram, producing very violent convulsions. Like quinotoxine it causes a slight rise of the blood pressure without affecting the rate; while cinchonine produces a fall of the blood pressure and an increase of the pulse rate. The convulsant action and the toxicity were confirmed by Biberfeld, who could not confirm the stimulating effect on the blood pressure.

Hildebrandt (**1908**) assumed that the toxicity of these compounds is determined by the existence of a free imido group in the piperidine ring. In experiments with frogs **methylcinchotoxine** was found to be less toxic than cinchotoxine; for tadpoles it was found to be slightly more toxic, and in mice it was distinctly more so. With oral administration to rabbits the toxicity was found to be less than that of cinchotoxine. **Thymylcinchotoxine** was said to be much less toxic than cinchotoxine, 3.5 grams causing no symptoms in a 2.5 kilogram rabbit. Hildebrandt also studied the **methylcinchotoxine iodomethylate.** In doses corresponding to those of cinchotoxine it causes dyspnea and later convulsions and death in mice, whereas cinchonine iodomethylate produces only a progressive depression. Of the methylcinchotoxine iodomethylate, 4.5 mg. causes paralysis in frogs of longer duration than was produced by the same dose of cinchonine

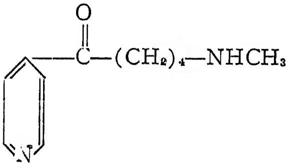
iodomethylate. Rusicka, Seidel and Liebel (1924) prepared a series of quinotoxine-like compounds of which the following have been studied in regard to their antiseptic action:



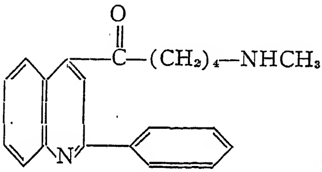
VIII
4-quinolyl-(ε-amino-pentyl) ketone



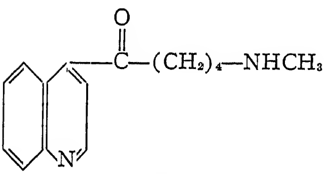
XI
4-(6-methoxyquinolyl)-(ε-aminopentyl) ketone



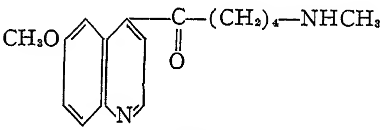
XXVII
4-pyridyl-(δ-methylaminobutyl) ketone



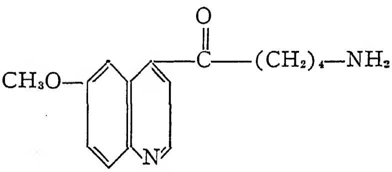
XXIX
4-(2-phenylquinolyl) (δ-methylaminobutyl) ketone



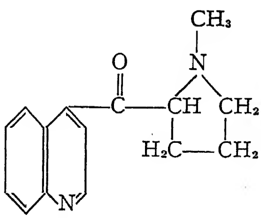
XXX
4-quinolyl-(δ-methyl-aminobutyl) ketone



XXXI
4-(6-methoxyquinolyl)-(δ-amino-butyl) ketone



XXXII
4-(6-methoxyquinolyl)-(δ-aminobutyl) ketone



XXI
4-quinolyl-α-(N-methyl-pyrrolidyl) ketone

The dihydrochlorides of Nos. VIII, XI, XXVII, XXIX, XXXI, and XXXII were tested by Giemsa in mice infected with nagana and recurrens but were found to have no curative

value. For colpidia they had not quite one-half the toxicity of quinine. The biological department of the Society for Chemical Industry in Basel reported that the dihydrochlorides of Nos. XI and XXX were only slightly toxic for paramecia as compared with quinine, No. VIII had about the same and XXI about one-fourth the toxicity of quinine.

From these reports it appears that the formation of toxines does not change the general pharmacologic properties (quinine-quinotoxine) materially; the antimalarial action, however, seems to be destroyed.

Meroquinene, which represents the piperidine compound characteristic for "toxines" with exception of the keto group, was studied by Grethe (1896). He found this substance itself and also the corresponding ethyl ester to be only slightly toxic for paramecia.

Heidelberger and Jacobs (1920) prepared a series of quinoline derivatives in which the quinuclidine ring is split as in quinotoxine but in which the keto group is reduced to an alcohol group. Some of these quinicinols, the **d-dihydroquinicinol** and the **d-N-methylquinicinol** were studied by Boyd (1926) with *Plasmodium praecox* in birds. He found the latter compound to be extremely toxic for these animals; the former though less toxic has marked hemolytic properties and neither one seems to be effective in bird malaria.

In order to render quinine more palatable, i.e., to suppress the bitter taste of the drug, several esters have been synthesized, which are more or less insoluble in water and consequently tasteless.

Euquinine, the quinine carboxylic acid ethyl ester, containing 82 per cent of quinine, has only a slightly bitter taste, it is practically insoluble in water but easily soluble in dilute acids.

Aristoquine, the diquinine carboxylic acid ethyl ester, containing 96 per cent of quinine, is said to be tasteless. Katz (1911) found that with aristoquine the excretion of quinine in the urine starts and increases more slowly than with quinine; after discontinuation of the drug the decrease of the excretion is also slower.

Saloquine is the quinine salicylic acid ester, the salicylate of which is marketed under the name of **Rheumatin.** Steel, Goerner

and Haley (1931) reported on a similar preparation, **quinine bi-salicylico-salicylate.**

Insipine, the sulfate of quinine diglycolic acid ester, is almost tasteless and practically insoluble in water, but it is more readily decomposed by diluted acids and alkalies than Aristoquine. Werner (1911) reported good clinical results especially in malaria of children, using doses of 1.5 to 2 grams, corresponding to 1 gram of quinine.

Quinine and urea hydrochloride ($C_{20}H_{24}O_2N_2HClCO(NH_2)_2HCl + 5H_2O$) forms colorless, translucent prisms or a white granular powder. It is odorless and has a very bitter taste. It is, however, very soluble in water (1 gram in 0.9 cc. at 24° C.) and therefore suitable for injections. Montmollin (1919) found that it has essentially the same pharmacologic action as quinine. In regard to its cardiac action it equals equimolecular quantities of quinine hydrochloride, it arrests the respiration in smaller doses, and with local application it is less toxic to the heart. It causes moderate but lasting anesthesia of the cornea without producing mydriasis.

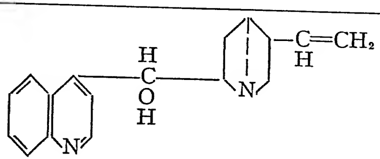
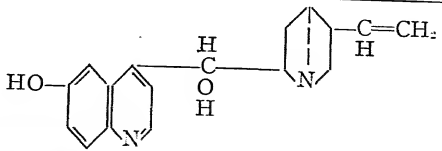
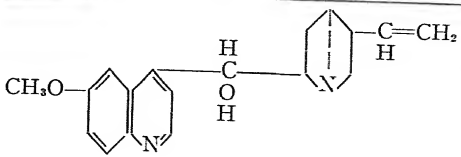
The report of Giemsa, Weise and Tropp (1926) that **acetylhydroquinine** has no antimalarial properties in malaria of birds, and the statement of Okamoto and Miura (1928) that it is very toxic and depressant for the isolated frog heart, is very interesting. Okamoto (1930) stated later that it is less effective in auricular fibrillation than either quinine or quinidine.

Stoute (1932) reported on the antimalarial properties of a preparation, **Tebetren,** which is a compound of quinine with methylacridine and dehydrocholic acid. Its action is said to be more rapid than that of quinine and it was found to be effective in benign and subtertian malaria. It is said to have little side action and to be also effective in quinine resistant patients.

The Relation between Chemical Constitution and Pharmacologic Action of Quinine and Its Derivatives

Table 13 gives a survey of the antimalarial properties of quinine and its derivatives as reported by Giemsa, Weise and Tropp (1926), Hegner, Shaw and Manwell (1928) and Goodson, Thomas and Macfie (1930). It contains also the partition coefficient between red blood cells and the solutions of these compounds as determined by Shaw (1928) and the trypanocidal action as collected from the reports of Cohn (1913) and of Morgenroth and

Table 13.—*Antimalarial, Trypanocidal, Toxicological and Physico-chemical Properties of Quinine and Its Derivatives.*

Compound	Antimalarial Action			Partition Coefficient Erythrocytes Solution	Trypanocidal Action	Skin Reaction in Quinine-sensitive Patients	Diffusion Velocity into Gelatin
	Giemsa	Hegner	Goodson				
 Cinchonine	±	++++	±	4.3	±	D −	++
 Cupreine	±	−	....	....	±	L +	....
 Quinine	++	++++	+	5.0	?	L +	+++

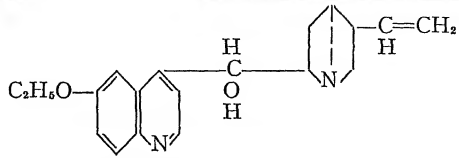
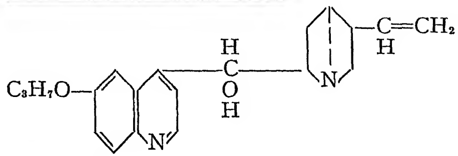
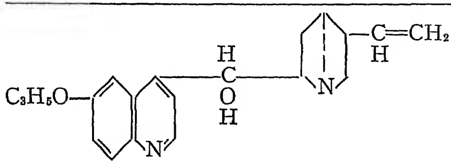
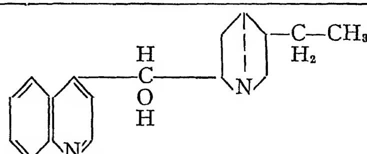
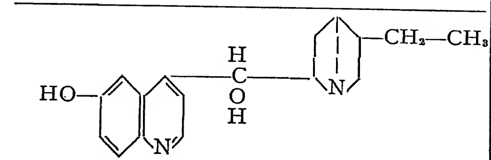
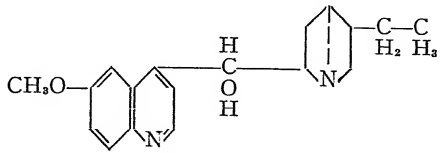
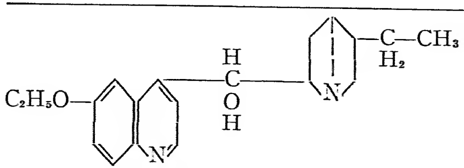
 Quinethyline	+++	....	....	....	....	....	....
 Quinpropyline	+	....	....	....	....	....	....
 Quinallyline	+	....	....	....	....	....	....
 Dihydrocinchonine	±	....	....	....	....	D —	....

TABLE 13.—*Antimalarial, Trypanocidal, Toxicological and Physico-chemical Properties of Quinine and Its Derivatives.*—(Continued)

Compound	Antimalarial Action			Partition Coefficient Erythrocytes Solution	Trypanocidal Action	Skin Reaction in Quinine-sensitive Patients	Diffusion Velocity into Gelatin
	Giemsa	Hegner	Goodson				
 Dihydrocupreine	++	....	....	4.0	....	L +	....
 Dihydroquinine	++	....	++	....	±	L +	....
 Ethylhydrocupreine	+±	+++	....	4.9	+	L +	....

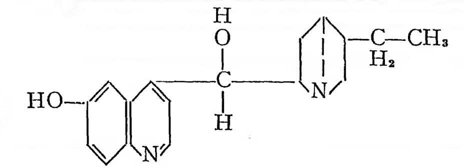
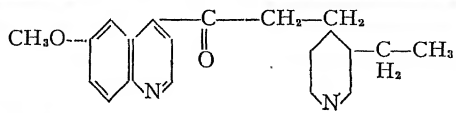
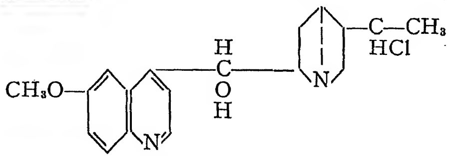
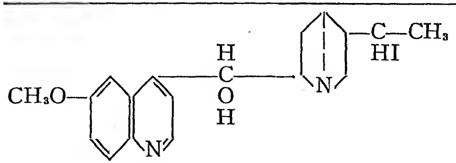
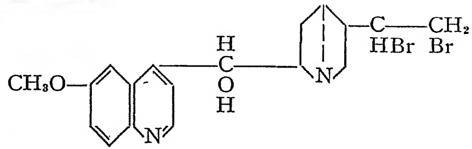
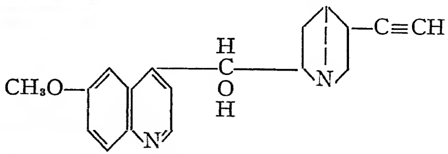
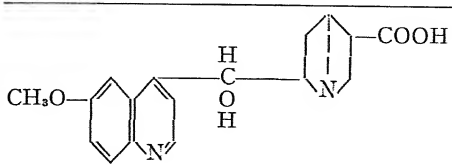
 Hydrocupreidine	....	....	....	5.0	....	....	....
 Hydroquinotoxine	....	++	....	5.4	....	....	....
 Hydrochloroquinine	++	....	....	....	....	....	....
 Hydroiodoquinine	±+	....	....	....	....	....	....

TABLE 13.—*Antimalarial, Trypanocidal, Toxicological and Physico-chemical Properties of Quinine and Its Derivatives.*—(Continued)

Compound	Antimalarial Action			Partition Coefficient Erythrocytes Solution	Trypanocidal Action	Skin Reaction in Quinine-sensitive Patients	Diffusion Velocity into Gelatin
	Giemsa	Hegner	Goodson				
 Dibromquinine	++	....	....	....	....	....	....
 Dehydroquinine	±	....	....	....	....	....	....
 Quitenine	0	....	....	0.3	....	0	....

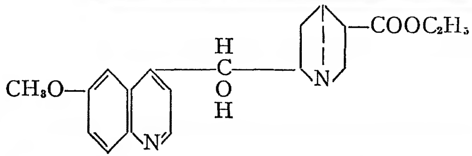
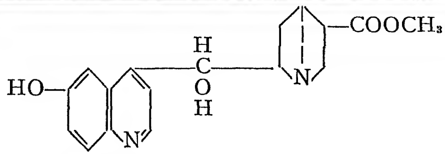
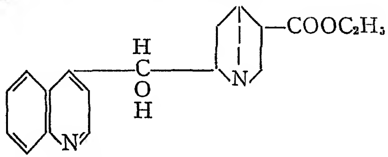
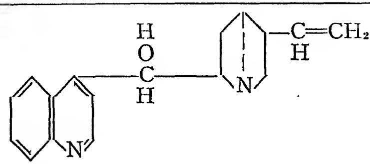
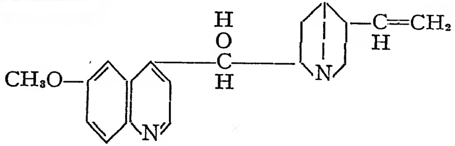
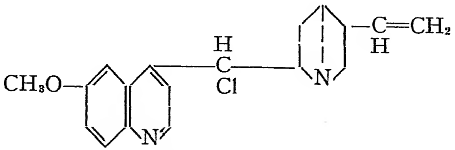
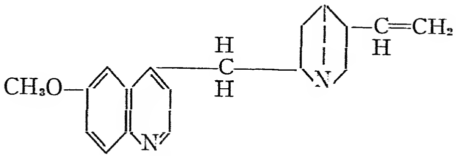
 Quitenineethylester	+	....	....	....	....	+	....
 Cupretininemethylester	....	....	....	2.9	....	....	....
 Cinchotenineethylester	....	++	....	1.9	....	....	....
 Cinchonidine	±	++++	±	3.5	....	L +	+

TABLE 13.—*Antimalarial, Trypanocidal, Toxicological and Physico-chemical Properties of Quinine and Its Derivatives.*—(Continued)

Compound	Antimalarial Action			Partition Coefficient Erythrocytes Solution	Trypanocidal Action	Skin Reaction in Quinine-sensitive Patients	Diffusion Velocity into Gelatin
	Giemsa	Hegner	Goodson				
 Quinidine	++	++++	+	4.4	?	D –	±
 Quininechloride	0	....	....	....	....	....	....
 Desoxyquinine	0	....	....	....	....	....	....

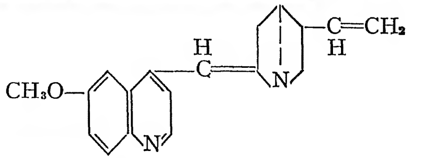
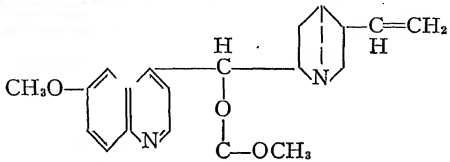
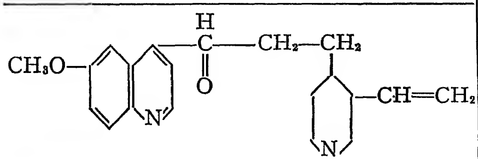
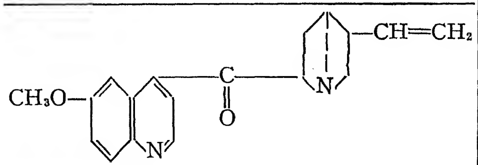
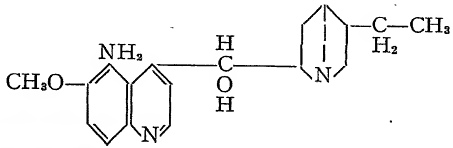
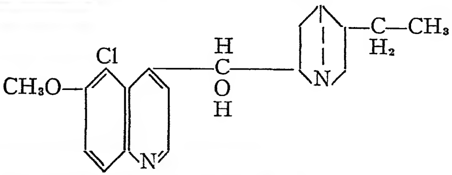
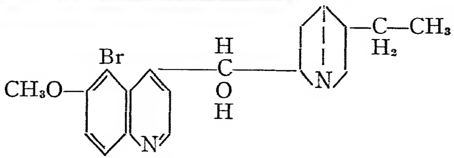
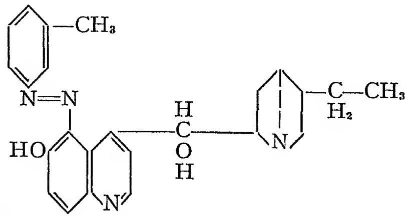
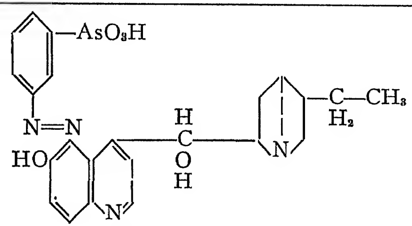
 Quinene	0	....	....	....	....	....	....
 Acetylhydroquinine	0	....	....	....	....	....	....
 Quinotoxine	0	+++	....	5.5	++	....	....
 Quininone	0	....	....	....	±	....	....

TABLE 13.—*Antimalarial, Trypanocidal, Toxicological and Physico-chemical Properties of Quinine and Its Derivatives.*—(Continued)

Compound	Antimalarial Action			Partition Coefficient Erythrocytes Solution	Trypanocidal Action	Skin Reaction in Quinine-sensitive Patients	Diffusion Velocity into Gelatin
	Giemsa	Hegner	Goodson				
29  5-Aminohydroquinine	++	....	....	....	....	....	....
30  5-Chlorohydroquinine	++	....	....	....	....	....	....
31  5-Bromohydroquinine	+	....	....	....	....	....	....

33  m-Tolylazohydro-cupreine	....	++	....	16.8	....	....	....
33  Phenyl arsonic acid azo hydrocupreine	....	0	....	0.0	....	....	....

his co-workers; it shows also the diffusion velocity into gelatine gels as determined by Kehar (**1930**) and the skin response of quinine-sensitive persons to the different compounds as reported by Dawson and Garbade (**1930**).

From Table 13 the following conclusions may be drawn as to the relation between the antimalarial action and the chemical constitution of quinine derivatives:

(a) **Methoxy group.** The methoxy group in the quinine molecule, although not essential, enhances the antimalarial action. (*Quinine; cupreine; cinchonine.*)

(b) **Homologs.** Replacement of the methoxy group by higher homologs such as ethoxy, propyloxy and allyloxy groups produces an improvement of the action only with the ethoxy group and further lengthening of the side chain decreases the action. (*Ethoxycinchonine; methoxycinchonine; propyloxycinchonine; allyloxycinchonine.*)

(c) **Vinyl group.**

(1) Hydrogenation of the vinyl group increases the antimalarial action (hydroquinine; quinine; hydrocupreine; cupreine). This effect is, however, not very marked, because hydrogenation does not produce any antimalarial properties when this is absent or only very weak in the original compound. (*Hydrocinchonine; cinchonine.*)

(2) Changing the double bond into a single bond by the addition of *hydrogen halides, ammonia* and *water* does not affect the antimalarial properties. (*Quinine; hydrochloroquinine; hydrobromoquinine; aminoquinine; hydroxyquinine.*) Therefore it appears that the vinyl group is not directly involved in the antimalarial action of quinine.

(3) **Changing the double bond in the vinyl group into a triple bond** renders the compound less stable and therefore less active. (*Quinine; dehydroquinine.*)

(4) **Oxidation of the side chain to a carboxyl group** renders the compound ineffective. (*Quinine; quitenine.*) Esterification of this carboxylic group makes the antimalarial action reappear. The antimalarial action of these esters is, however, less marked than that of quinine, presumably on account of the reformation of the carboxylic group by saponification. (*Ethylquitenine; quitenine.*)

(d) **Stereoisomerism around the secondary alcohol group.** This has no material influence on the antimalarial properties of quinine. (*Quinine; quinidine.*)

(e) **Chemical changes of the secondary alcohol group.**

(1) Replacing the hydroxyl radicle by chlorine or hydrogen or splitting off one molecule of water abolishes the antimalarial action completely. The same holds true for acetylization. (*Quininechloride; desoxyquinine; quinene; acetylquinine.*)

(2) Giemsa observed that replacing the hydroxy group by oxygen (*quininone*) or simultaneous splitting of the nucleidine ring (*quinotoxine*) abolishes the antimalarial action.

(f) **Substitution in the 5- position of the quinoline ring.** Substitution of the 5-hydrogen atom in the quinoline ring by an amino group or by halogen does not materially affect the antimalarial action. (*5-Aminohydroquinine; 5-bromohydroquinine; quinine.*)

Introduction of an azo group in this position does not affect the antimalarial action; but this is destroyed by the introduction of phenylarsonic acid which liberates ions at pH 7.4.

Shaw believed that the comparatively small toxicity of quinine for plasmodia *in vitro* suggests that the site of the action is within the red blood cell perhaps in the moment of sporulation. In order to be effective in such a way, the drug must be able to penetrate the erythrocytes besides having antiplasmodial properties. He therefore made determinations of the partition coefficient between red blood cells and the solutions of the alkaloids, as pointed out in the text and given in the table. The results of these experiments as to the relation between chemical constitution and the ability to penetrate the cells may be summarized as follows:

(a) Removal of the methoxy group produces only a slight reduction of the partition coefficient. (*Quinine; cinchonine.*)

(b) The higher homologs have not been studied in this regard.

(c) Hydrogenation of the vinyl group has no effect on the partition coefficient.

(d) Saturation of the vinyl group by hydrogen haloids has not been studied.

(e) Nor has the effect of the change of the double to a triple bond been investigated.

(f) Oxidation of the side chain produces complete loss of the ability to penetrate. This is partly but not completely restored by esterification.

(g) Stereoisomerism around the secondary alcohol group has no marked effect on the partition coefficient, although a slight reduction is noticeable. (*Quinine; quinidine; cinchonine; cinchonidine.*)

(h) Chemical changes of the secondary alcohol group with simultaneous rupture of the nucleidine ring has no marked effect on the partition coefficient.

(i) Introduction of azo dyes into the 5- position of the quinoline ring increases greatly the partition coefficient; introduction of azo groups containing an ionic group capable of yielding ions at a pH 7.4, yield a compound which is completely unable to penetrate the cells.

(k) Conversion of the nitrogen of the quinuclidine ring into a quaternary base results in complete loss of ability to penetrate the cells. Such compounds were also tested by Hegner, Shaw and Manwell and found to be ineffective in malaria of birds. From this it appears that there is a certain parallelism between the antimalarial action and the ability to penetrate the cells.

Column III of the table shows that the antimalarial action of the cinchona alkaloids does not parallel the trypanocidal activity. The trypanocidal action of quinine and quinidine is rather uncertain; the hydrogen compound is slightly more effective. Hydrochloroquinine was found to be ineffective, although its antimalarial action is about as good as that of quinine. On the other hand, quinotoxine which Giemsa found ineffective in bird malaria, was very effective in trypanosomiasis, and the same holds true for the ineffective quininone but to a lesser degree.

It appears, therefore, that the trypanocidal action follows different laws, as will be discussed more in detail in connection with the acridine dyes.

The results of Kehar concerning the ability of cinchona alkaloids to penetrate into gelatin gels show a somewhat different picture as to the relation between this action and the antimalarial properties than that expected from the partition coefficient. It may be possible that his results are impaired by the fact that he used different salts, the anions of which, according to his own findings, would also influence the penetration. (*Quinine bihydrochloride; cinchonine monohydrochloride; cinchonidine sulfate; quinidine base.*)

Another essential point in the relation between pharmocologic action and chemical constitution is the response of quinine-

sensitive persons to different cinchona alkaloids by irritation of the skin. It has been known since Pasteur's classical work on tartaric acid that certain organisms may destroy one optical isomer faster than the other and similar conditions may be involved in quinine hypersensitivity. The fourth column of the table refers to the response of quinine-sensitive persons to cinchona alkaloids as given by Dawson and Garbade (1930). Such persons respond with a positive skin test to hydroquinine, cinchonidine, hydrocinchonidine, cupreine, hydrocupreine and ethylhydrocupreine, all of which are levorotatory, while the response to quinidine, cinchonine, hydrocinchonine, ethylhydrocupreidine, hydrocupreidine and ethyl quitenidine—all dextrorotatory drugs —was negative. Aside from the inability of the organism to destroy the levorotatory compounds other factors may enter into this phenomenon. Thus, for instance, a quinine-sensitive person did not respond to quitenine, a levorotatory compound. We have seen above that this compound cannot penetrate the cells while the corresponding ethylester can do so and also produce a positive skin reaction. Finally Dawson and Garbade have also demonstrated that the idiosyncrasy to levorotatory compounds does not extend to levorotatory substances with a long side chain, such as eucupine (isoamylhydrocupreine) and vuzine (isooctylhydrocupreine). It extends only to members of the same series of lower molecular weight than isoamylhydrocupreine. It is also interesting that the skin test was negative with 5- nitro and amino substituted derivatives of these levorotatory substances; this may also be due to diminished ability to enter the cells. The same holds perhaps also true for hydrochloroquinine, although its penetration into the cells has not been studied. From this it may be seen how important the physico-chemical properties of a compound and their changes may be for the pharmacologic action of a drug.

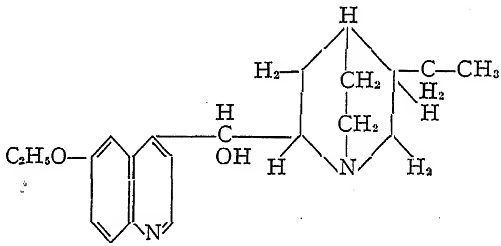
Chapter IX.

Hydrocupreine Derivatives.

In the following we shall discuss a series of hydrocupreine derivatives. These may be considered in a group by themselves because they have distinct antiseptic properties which are more pronounced than in the cinchona alkaloids.

Optoquine.

Ethylhydrocupreine,



the higher homolog of hydroquinine, is marketed under the name of **Optoquine.** It is a faintly yellowish-white, amorphous and odorless powder, which has a bitter taste. It is almost insoluble in water and is more or less soluble in organic solvents and in diluted acids.

Ethylhydrocupreine has marked *antiseptic properties,* and also inhibits fermentative reactions like quinine. Morgenroth and Halberstaedter (**1911**) claimed that it is more active than quinine in trypanosome infections, which was not confirmed for nagana infections by Cohn (**1913**). Morgenroth and Levy (**1911**) found that its antiseptic action against pneumococci is much more marked than that of hydroquinine, that a prophylactic injection may protect the animals against infection and that it may save a great number of animals even if administered five to six hours after

the infection. In a later publication Morgenroth and Bumke (1914) showed that this action is most marked with ethylhydrocupreine, the isopropyl compound being one-half to one-fourth as effective, the isoamyl-compound having one-twentieth the efficiency and the action of quinine being one-hundred-fiftieth that of optoquine. Later Morgenroth (1914) tested a great number of different strains of pneumococci, which were all sensitive to the drug, and he believed it improbable, therefore, that an optoquine resistant strain would be encountered. Moore (1915) confirmed the high sensitivity of pneumococci as compared with other germs and considered the optoquine action so specific that it may be used for the identification of these organisms. Cohen, Kolmer and Heist (1917) found that serum reduces the efficiency of optoquine to from one-fifth to one-tenth and Morgenroth found that in the presence of blood it is even less effective against pneumococci, the red blood cells having a greater bactericidal action than the serum on account of the adsorption of the drug by the former. Baermann (1914) used ethylhydrocupreine in malaria without satisfactory results, the action being not lasting and relapses, therefore, more frequent than with quinine. Schaeffer (1917) found it effective against diphtheria bacilli and Friedmann (1916) reported favorable results from intralumbar injections in epidemic meningitis. In the years following the introduction of the drug by Morgenroth a great number of clinical papers were published on its action in different infectious diseases and especially in pneumonia. This literature is discussed extensively by Laqueur (1923). But the opinions on its value were divided, and Heffter (1921) stated that just those clinicians who have treated the greatest number of pneumonia patients with optoquine confess that there is no proof of an etiotropic action of the drug and that there is hardly a reduction of the duration of the disease. Favorable effects on the euphoria and on the temperature may be observed only with early administration.

Smith and Fantus (1916) were the first to publish a *pharmacologic study* on the action of optoquine. They found its antipyretic action in experimental fever of rabbits less marked than that of quinine. With intravenous administration they observed a fall of blood pressure, which was less marked than with corresponding doses of quinine; the depressant action on the heart, however, was more marked. This was confirmed by ten

Doerschate and Storm van Leeuwen. But their dose of 5 mg. per rabbit, given intravenously, would correspond to the tremendous dose of 175 to 200 mg. in man. The clinical dose with oral administration is 6 times 0.25 gram and we shall see that special precautions are necessary to secure a slow absorption in order to avoid undesirable side actions. The dose used by ten Doerschate and van Leeuwen and also that of Smith and Fantus is therefore too high to allow comparison with the effect of therapeutic doses given orally in man.

Hirschfelder (1915) found that optoquine causes constriction of the cerebral and retinal vessels. This was generally confirmed by Smith and Fantus (1916), who assumed that this vasoconstriction counteracted to a certain extent the cardiac depression and that, therefore, the control of the blood pressure would not be an adequate index for the toxic action on the heart.

Smith and Fantus (1916) also found that 2 per cent solutions produce a marked irritation of the rabbit cornea, while Morgenroth and Ginsberg (1913) using 1 to 1.25 per cent solutions observed marked local anesthetic action, optoquine being in this respect 2.5 to 3 times more effective than quinine.

Berger (1926) reported that optoquine is adsorbed by the red blood cells. This was also the assumption of Schnabel (1920), who studied this mechanism more closely. He found that the optoquine level in the blood decreases rapidly after intravenous administration. After the minimum has been reached there is again a slight increase followed by a slow decrease. He believed the secondary rise to be due to liberation of optoquine from the cells. Morgenroth (1914) had reported that optoquine disappears so rapidly from the circulation that from ten to forty-five minutes after the intravenous injection less than one-fortieth of the amount injected was found in the blood.

A fraction of optoquine seems to be excreted by the bile, because Kauftheil and Neubauer (1926) found that after intravenous injection of the drug the bile acquired moderately antiseptic properties.

According to Ikeda (1916) optoquine has not the marked effect of quinine on the emigration of leucocytes. Dixon and Premankur (1927) found that concentrations of 1 : 400 cause hemolysis.

Scheinfinkel (1929) reported that optoquine in concentrations of from 1 : 10,000 to 1 : 5000, in common with other capillary

active substances, produces an increase of the excitability of the nerve in the neighborhood of the cathode.

Chopra, Dikshit and David (1928) reported that the effect of optoquine on the uterine muscle is less marked than that of quinine. Murakami (1930) confirmed this for the uterus and found that it also causes contractions of the Fallopian tubes, of the round ligament and of the vagina of the rabbit. He stated that, in contrast to quinine, optoquine does not antagonize the effect of epinephrine on these organs.

The *toxicity* of the drug is very much greater than that of quinine (Dixon and Premankur, 1927). Baermann (1914) considered the side actions, such as vertigo and vascular disturbances, prohibitive for further clinical use in malaria. Reports on visual disturbances after the clinical use of optoquine were published soon after the introduction of the drug. Morgenroth (1914) believed that this amblyopia would disappear sooner or later when the drug was discontinued, as is the case after quinine. In the following years with more extensive use of optoquine, a considerable number of more or less severe visual disturbances were, however, reported. They are reviewed by Laqueur (1923), who reached the conclusion that in most cases more than the advocated dose was used; that symptoms are not always slight and of short duration; and that the disturbances may increase rapidly, leading to amblyopia and even amaurosis. This is usually bilateral and combined with mydriasis and suppression or reduction of the light reaction, usually without affecting the functionation of the musculature of the eye ball. The ophthalmoscopic picture of early cases shows blurring of the papilla, constriction of the retinal vessels, disappearance of the pressure pulse and occasionally reddening of the macula. Morgenroth (quoted from Laqueur) believed that the eye effects can be avoided by observing the following directions:

(1) Use of difficultly soluble preparations such as optoquine base, optoquine tannate, optoquine salicylate. He advised that the use of the hydrochloride be avoided.

(2) To reduce the effect of the hydrochloric acid of the stomach by giving the drug only on a full stomach, preferably in milk.

(3) To avoid a large single dose and to give small doses of 0.12 to 0.2 gram every 4 hours, also during the night, and not to exceed a total of 1.2 gram per day.

(4) Careful observation of the patient for the occurrence of visual disturbances.

The toxine corresponding to optoquine, **ethylhydrocupreinotoxine,** has, according to Morgenroth and Bumke (**1914**), no specific antiseptic properties whatever. Dixon and Premankur (**1927**) found it three and one-half times more toxic than quinine for paramecia, also more toxic for smooth and striated muscle and much more toxic for sympathetic ganglia and for the isolated frog heart. The hemolytic action was also more marked.

Isopropylhydrocupreine, the next higher homolog of optoquine, was tried by Baermann (**1914**) in malaria in doses of 0.2 gram 3 to 4 times daily for from 2 to 5 days. He found it distinctly antimalarial, but the action is somewhat delayed and the effect not lasting, because the parasites reappear immediately after discontinuation of the drug. This is in accordance with the findings of Giemsa, Weise and Tropp (**1926**) that even the next lower homolog, ethylhydrocupreine, shows a reduction of the antimalarial properties as compared with methylhydrocupreine. The disinfectant action of isopropylhydrocupreine for diphtheria bacilli has been studied by Braun and Schaeffer (**1917**) and found to be inferior to that of the higher homologs. Its efficiency against staphylococci, according to Morgenroth and Tugendreich (**1916**) is twice as marked as that of optoquine. Morgenroth and Bumke (**1918**) determined its efficiency against pneumococci as one-half to one-fourth less than that of optoquine. Its local anesthetic action was found to be more marked than that of ethylhydrocupreine (Morgenroth and Ginsberg, **1913**). In its toxicity for cilia, striated muscle, the isolated frog heart and in its hemolytic action it ranges between the lower homologs, quinine and optoquinine, and isoamylhydrocupreine, the latter being the most toxic (Dixon and Premankur, **1927**).

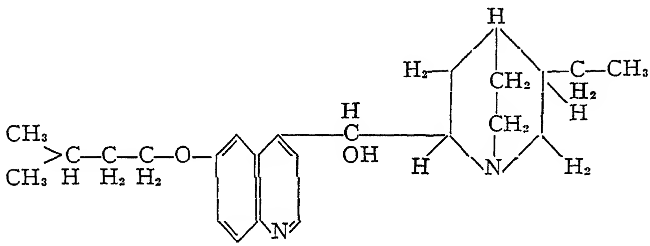
The corresponding unsaturated compound, **allylhydrocupreine,** is reported to be less toxic for paramecia than quinine. Its depressant action on the intestine as well as on the sympathetic ganglionic cells is slightly more marked (Dixon and Premankur, **1927**).

The same investigators found **benzoyl-isopropylhydrocupreine** to be but slightly toxic for paramecia, markedly so for plain muscle, and slightly depressant for the sympathetic ganglionic cells.

Isobutylhydrocupreine is, according to Morgenroth and Tugendreich (1917), eight times as effective as ethylhydrocupreine against *Staphylococcus aureus,* and according to Schaeffer (1917) against diphtheria bacilli. Morgenroth and Ginsberg (1913) found the local anesthetic properties of isobutylhydrocupreine equal to those of the next higher homolog, being from 20 to 25 times more effective than cocaine when tested on the rabbit cornea.

Eucupine.

Isoamylhydrocupreine, Eucupine,



may be prepared like the other homologs of this series according to D.R.P. 254,712 Kl. 12p (1911). It is a white tasteless powder insoluble in water and benzene, but easily soluble in alcohol, ether, chloroform and hot fatty oils. The hydrochloride forms fine needles of acid reaction and bitter taste soluble in fifteen parts of water and easily soluble in alcohol.

Isoamylhydrocupreine was found by Morgenroth and Tugendreich (1917) to be from 10 to 12 times more effective as to its *antiseptic action* than ethylhydrocupreine against staphylococci and streptococci. Morgenroth and Bieling (1917) also found it very effective against tetanus bacilli and *Bacillus gangrenosus.* According to Schaeffer (1917) it is more effective against diphtheria bacilli than is isopropylhydrocupreine. Its antiseptic value against pneumococci, however, is but one-twentieth that of ethylhydrocupreine. Bijlsma (1920) found it less effective than isooctylhydrocupreine against *Bacillus tetragenus.* He also stated that the antiseptic action of solutions of isoamylhydrocupreine is decreased by standing and by physiologic saline. Red blood cells and 10 per cent of serum also decrease the efficiency. Baermann (1914) believed it to be of little value in the treatment of malaria. Its clinical usefulness in staphylococcus and streptococcus infec-

Visual disturbances are less common with eucupine than with optoquine. According to Laqueur disturbances such as reported by Traube and Hegler (**1920**) may occur without the administration of the drug.

Eucupinotoxine, the toxine corresponding to isoamylhydrocupreine, has, according to Morgenroth and Bumke (**1914**) and Morgenroth and Bieling (**1917**), a stronger and more rapid action than the mother substance. Against *Bacillus gangrenosus,* however, Bieling (**1917**) found it inferior to eucupine. Dixon and Premankur (**1927**) consider it much more toxic than the isoamylhydrocupreine and the lower homologs for paramecia, smooth muscle, the sympathetic ganglionic cells and the heart. Its hemolytic action and its local anesthetic properties are also said to be more marked.

Benzoyl-isoamylhydrocupreine was studied by Dixon and Premankur (**1927**). They found it very toxic for paramecia, smooth muscle and the sympathetic ganglionic cells.

Hexylhydrocupreine. Morgenroth and Tugendreich (**1917**) found that this compound is about as effective as isoamylhydrocupreine against *Streptococcus longus.* Schaeffer (**1917**) found the same true for diphtheria bacilli; both compounds proved more effective than the lower homologs up to isopropylhydrocupreine as well as the higher homologs, decyl- and dodecylhydrocupreine.

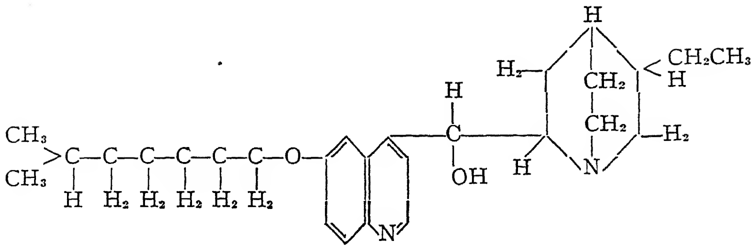
Heptylhydrocupreine. According to Morgenroth and Tugendreich (**1917**) heptylhydrocupreine is as effective as isoamylhydrocupreine against *Streptococcus longus;* but against *Staphylococcus aureus* it is about three times more effective than the latter. Schaeffer (**1917**) found it superior to hexylhydrocupreine toward diphtheria bacilli.

Isoheptylhydrocupreine. This compound was studied by Chopra, Dikshit and David (**1928**) on uterine contractions. They found that it had little effect on the isolated uterus, but the nonpregnant multiparous uterus and the pregnant uterus showed some stimulation.

N-octylhydrocupreine. This has about the same effect as the heptyl compound against the diphtheria bacillus (Braun and Schaeffer, **1917**) and against *Streptococcus Aronson* (Morgenroth and Tugendreich, **1917**).

VUZINE.

Isooctylhydrocupreine, vuzine,



may be prepared in the same manner as eucupine. It forms colorless crystalline needles, easily soluble in warm water, alcohol and chloroform; less soluble in ether, benzene and hydrochloric acid. The aqueous solutions of the salts have an acid reaction.

Advocated by Morgenroth, like eucupine, vuzine has been used as an *antiseptic* especially in gas gangrene. Braun and Schaeffer (1917) thought it equal to the heptyl compound in disinfectant action and slightly superior in antiseptic effect. Morgenroth and Bieling (1917), as well as Morgenroth and Tugendreich (1917) found it to be optimal against *Bacillus gangrenosus* and *Streptococcus longus.* Bieling (1917) observed that it neutralizes the toxins of *Bacillus gangrenosus.* Morgenroth and Abraham (1920) found that the injection of solutions of 1:2000 protects mice against streptococcus infections. The efficiency varies considerably with the organism, however. This was demonstrated by Kaufmann (1919), who found that vuzine is more effective against streptococci, less against *Staphylococcus albus,* and only moderately so against *Staphylococcus aureus.* The clinical usefulness has been extensively discussed by Laqueur (1923). Although many clinicians, like Rosenstein (1920), reported good results with systemic administration, it appears that the systemic action is not very reliable (Klose, 1919); Specht (1920) expressed the same opinion, although he found it valuable in local infections. This was also emphasized by Keysser (1919), but the latter also pointed out that more or less marked injury of the tissue may be produced by the drug. This was confirmed by Bijlsma (1920) in animal experiments. Morgenroth (1917) and Kaufmann (1919) had found, as was confirmed by Bijlsma (1920), that vuzine is less effective in the presence of ascitic fluid and serum. Keysser (1919) found that vuzine solutions,

1 : 10,000, produce a precipitate of basic vuzine with serum, that such solutions hemolyze red blood cells and that they depress phagocytic processes considerably. He also pointed out that the disinfection of pus required concentrations as high as 1 : 5000, which was confirmed by others. This is in accordance with the observations of Bijlsma that infected tissue is not sterilized even when comparatively strong solutions are used.

Bijlsma (1920), who studied the *pharmacology* of vuzine, determined the minimal fatal dose with subcutaneous injections as 200 mg. per kilogram for mice and cats. Hofmann (1918) had found that the intravenous injection of 15 mg. per kilogram is fatal in rabbits, 35 mg. killing the animals immediately by cardiac failure. Bijlsma found vuzine distinctly more toxic than eucupine, although the fatal concentration for both drugs is the same, the heart being arrested in systole. The intravenous injection produces a fall of blood pressure, due to weakening of the cardiac muscle, dilatation of the coronary arteries and temporary peripheral vasodilatation. Similar results were reported by Hofmann (1918) for rabbits. He emphasizes the short duration of this fall of blood pressure which is combined with a slowing of the pulse rate and an increase of the amplitude. This phenomenon persists when the vagi have been severed. The effect on the isolated blood vessels differs somewhat from that of eucupine. Bijlsma (1920) found that vuzine produces vasoconstriction, while eucupine causes vasodilatation; both, however, constrict the pulmonary and dilate the coronary arteries. It has been mentioned that vuzine solutions hemolyze erythrocytes, which action is distinctly diminished by the presence of serum. Like eucupine it changes the blood pigment and is also bound to the red blood cells. This binding, according to Berger (1926), is more stable than that observed with eucupine. *In vitro,* such saturated red blood cells still show marked antiseptic properties, but they are ineffective when injected into animals infected with streptococci.

Vuzine has marked *local anesthetic properties* as pointed out by Morgenroth and Ginsberg (1913) and later by Bijlsma (1920) and others, both for rabbit's cornea and nerve (frog's sciatic). Concentrations of 1 : 100, however, produce severe injury of the cornea.

Vuzine stimulates the respiratory center, but does not affect the vagus center, at least in cats. In higher concentrations it produces in irreversible paralysis of striated muscle, but according

to Dixon and Premankur (1927) it is inferior to eucupine in this respect.

Bijlsma (1920) found the *antipyretic properties* of vuzine more marked than those of eucupine in experimental coli fever and also in fever produced by the corresponding toxines.

The absorption after intramuscular and subcutaneous injection is rather slow, for some of the material may be detected at the site of the injection as late as 4 days afterwards. After intravenous injection of almost fatal doses of the dihydrochloride, only one-half could be isolated from the blood after 35 minutes, the rest being adsorbed by the organs, heart, liver, kidney, adrenals, brain, spinal cord and muscle. Twenty-four hours later only mere traces may be recovered from these organs. The distribution of vuzine between corpuscles and serum is such that the former contain from 7.7 to 16.6 times more than the latter. Boecker (1920) found that even the most soluble salts are only slightly absorbed from the intestinal tract. His findings agree with those of Bijlsma that most of the absorbed material is fixed in the organs and that only very small quantities, if any, are excreted with the urine. He assumed that the larger portion is destroyed in the organism, to a greater extent than quinine. There is evidently also no material excretion with the bile, since Kauftheil and Neubauer (1926) found that after intravenous administration neither vuzine nor eucupine render the bile antiseptic.

Kaufmann (1919) studied **isooctylhydrocupreinotoxine, vuzinotoxine,** as to its antiseptic properties. He found it superior to the mother substance in regard to the velocity of its action.

Decylhydrocupreine is less effective against diphtheria bacilli than the octylhydrocupreine, according to Braun and Schaeffer (1917). The same was found by Morgenroth and Tugendreich (1917) for *Staphylococcus aureus* and *Streptococcus longus,* and by Bieling (1917) for anthrax and tetanus.

Dodecylhydrocupreine. Braun and Schaeffer (1917) found this to be even less effective than the decyl compound against diphtheria bacilli. Bieling (1917) found the same for anthrax and tetanus and Morgenroth and Tugendreich (1917) for *Staphylococcus aureus* and *Streptococcus longus.*

Cetylhydrocupreine, according to Braun and Schaeffer (1917), has only very little effect on diphtheria bacilli.

Morgenroth and Tugendreich (1917) studied also a hydrocupreine derivative in which the hydrogen of the hydroxy group

was replaced by the radicle $O—CH_2—CO$. This **phenacylhydrocupreine** killed one streptococcus strain in a concentration of 1:20,000.

RELATION BETWEEN CHEMICAL CONSTITUTION AND PHARMACOLOGIC ACTION OF HYDROCUPREINE DERIVATIVES.

It has been stated in the foregoing discussion that the antiseptic action of the different hydrocupreine derivatives varies considerably.

Chart 1 is based on the experiments of Braun and Schaeffer

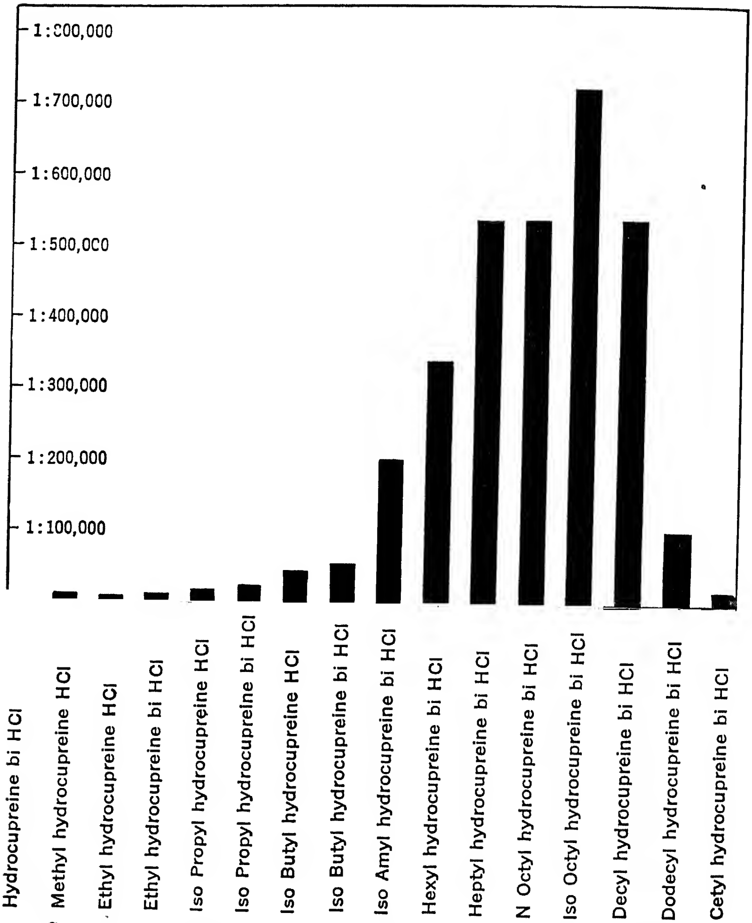


CHART 1.—Antiseptic Effect of Hydrocupreines on *Bacillus Diphtheriae*. (Braun and Schaeffer)

(1917) on the antiseptic action of these compounds against diphtheria bacilli. It shows that starting with isopropylhydrocupreine dihydrochloride there is a marked increase of the antiseptic action culminating with isooctylhydrocupreine, the higher homologs showing a very marked and rapid decrease of efficiency with in-

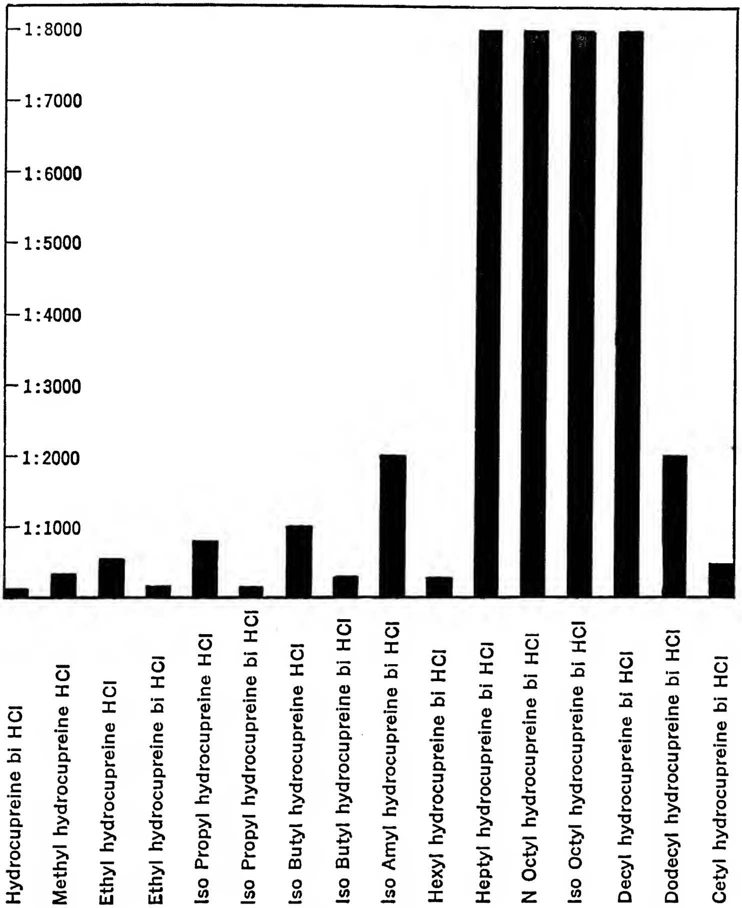


CHART 2.—Disinfecting Effect of Hydrocupreines on *Bacillus Diphtheriae.* (Braun and Schaeffer)

creasing molecular weight. Chart 2 illustrates the disinfectant action of the same compounds against the same organism, studied by the same authors.

The sequence of the efficiency is about the same as with the antiseptic action. The disinfectant action of the isooctyl com-

pound is, however, not so outstanding, inasmuch as heptyl, n-octyl and decylhydrocupreine have the same disinfectant value. Furthermore it demonstrates that the ethyl, isopropyl, isobutyl and isoamyl compounds which were used in the form of mono- and dihydrochloride always show a lower disinfectant value in form of the dichloride than as the monochloride. The reason for this phenomenon will be discussed further below.

Chart 3 is based on the work of Morgenroth and Bumke and of Morgenroth and Tugendreich.

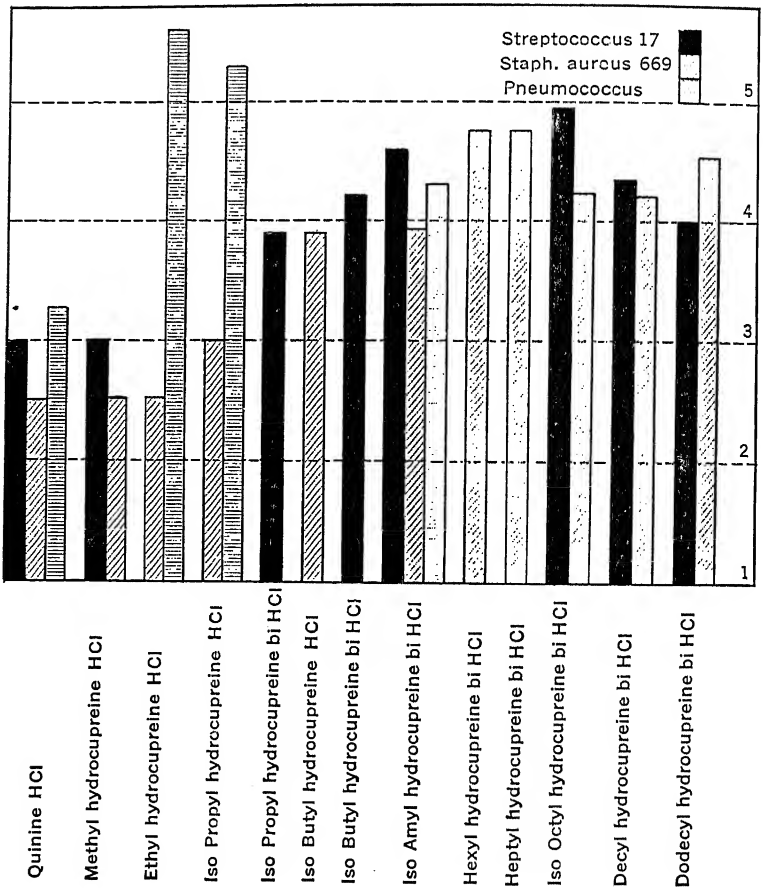


CHART 3.—Antiseptic Effect of Hydrocupreines against Different Organisms. (Morgenroth and Bumke, Morgenroth and Tugendreich)

This chart gives the logarithmic values of the antiseptic concentrations as determined by Morgenroth and Bumke and Morgenroth and Tugendreich for Streptococcus 17, Staphylococcus 669, and Pneumococcus.

It illustrates the efficiency of the hydrocupreine derivatives against pneumococci, *Staphylococcus aureus 669* and against *Streptococcus 17.* It may be seen that the optimal efficiency against these organisms occurs with different preparations. It shows that ethylhydrocupreine is maximally effective against pneumococci, that heptylhydrocupreine has a marked effect on *Staphylococcus aureus* and that isooctylhydrocupreine has marked antiseptic properties for *Streptococcus 17.* Thus it becomes manifest that there must be some relation between certain organisms and certain compounds.

On the other hand, Chart 4 shows that isooctylhydrocupreine

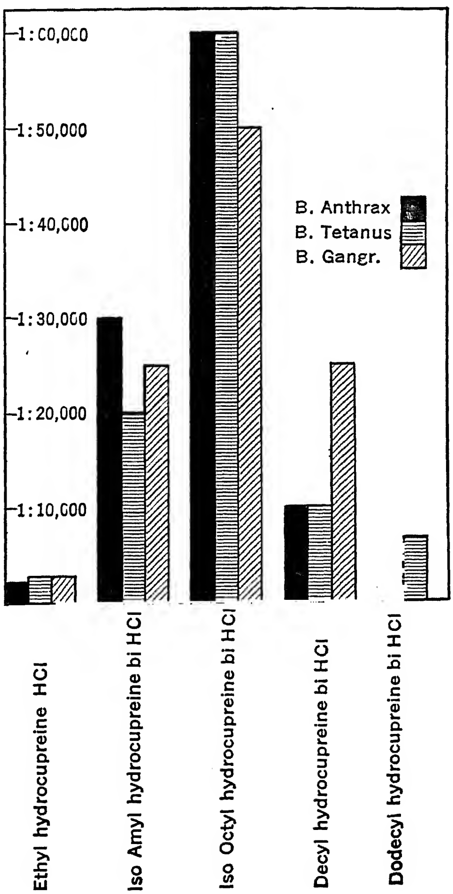


CHART 4.—Antiseptic Action of Hydrocupreines on Different Bacilli. (Bieling and Morgenroth and Bieling)

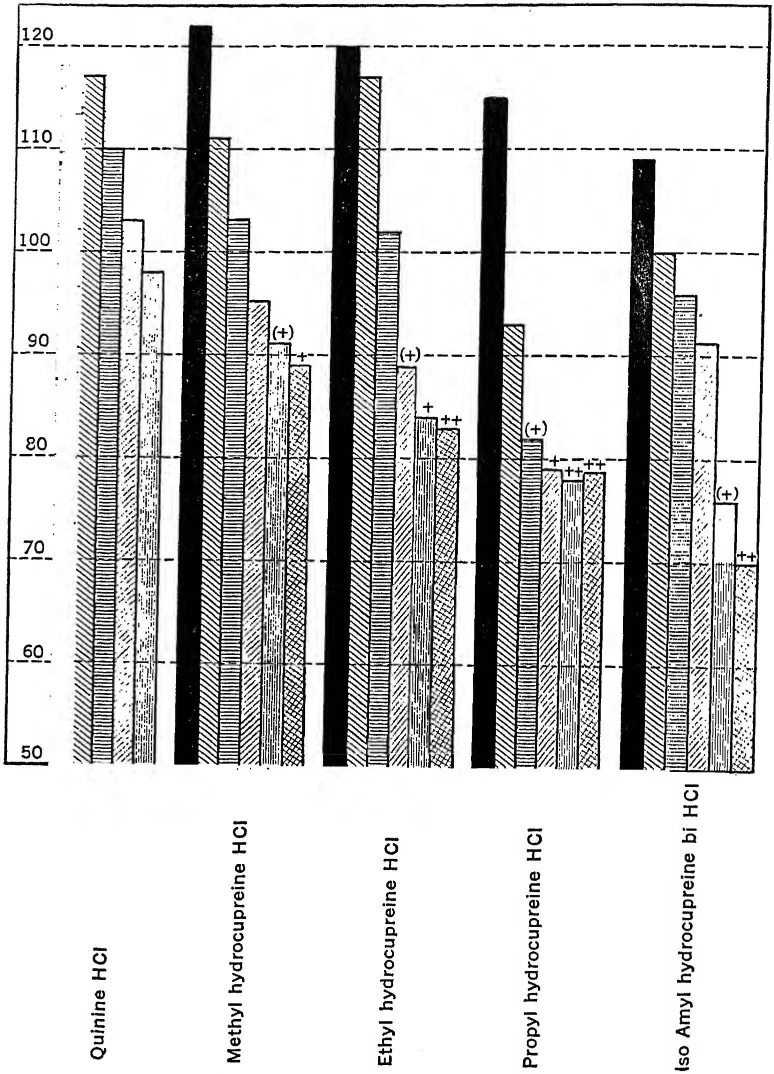


CHART 5. See caption on right-hand page.

Chart illustrates the effect of the addition of various quantities of a 0.2 per cent solution of sodium carbonate to 10 cc. of a 0.1 per cent solution of the hydrocupreine derivatives. The surface tension was determined by means

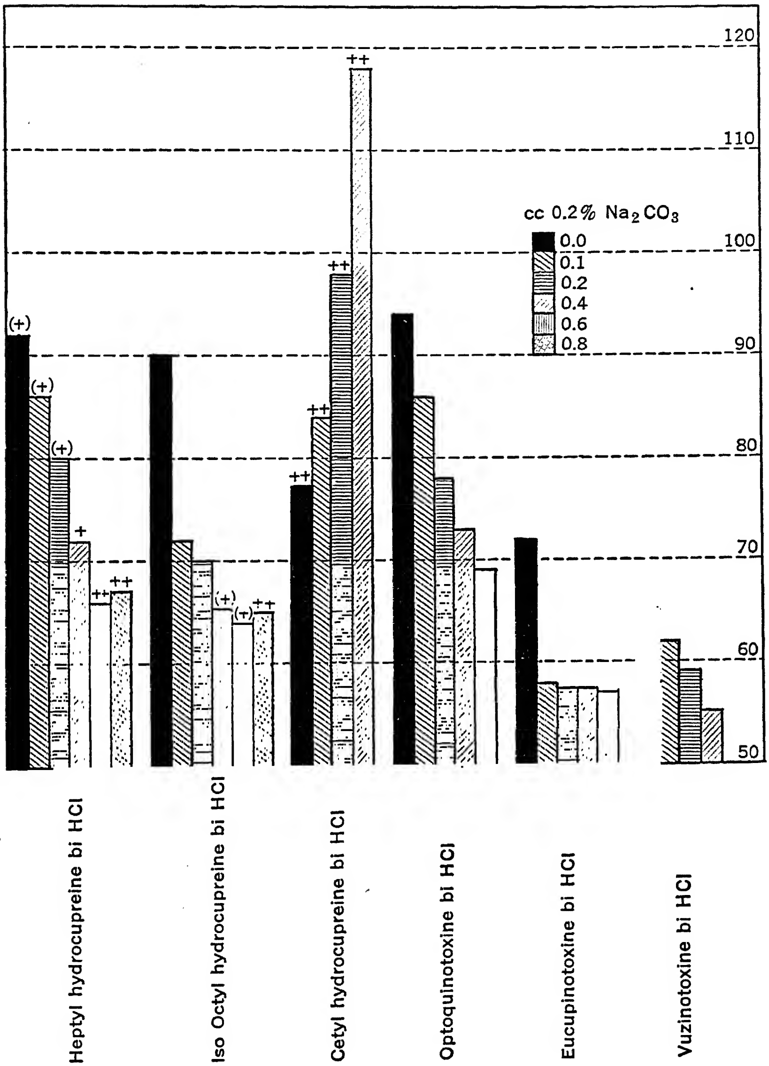


CHART 5.—Effect of Addition of Alkali on the Surface Tension of 0.1 Per Cent Aqueous Solutions of Hydrocupreine Derivatives. (J. Traube)

of the "Viscostalagonometer" of Traube (the value of water being 121). The symbol (+) indicates weak opalescence, + opalescence, + + marked opalescence.

is maximally effective against diphtheria, anthrax, tetanus and bacillus gangrenosus as found by Schaeffer, by Bieling and by Morgenroth and Bieling. This illustrates that compounds may be synthesized in which the specific effect is not limited to one group of microorganisms but which show a marked effect with a number of different germs.

Morgenroth (Morgenroth, Schnitzer and Rosenberg, 1921), therefore, reported his experiences as follows:

(1) Members of homologous series which do not show very marked differences in test tube experiments may prove quite different when tested in animal experiments against the same organisms.

(2) Effective compounds of optimal efficiency in test tube experiments may be much less effective in animal experiments than others.

(3) Such compounds which are found very effective both *in vitro* and *in vivo* against one strain may vary considerably as to their efficiency against other strains of the same organism.

(4) One substance may show great variations of its efficiency against the different strains *in vivo,* although *in vitro* it is found to be uniformly effective.

For these reasons the antiseptic value of a compound should be decided by a great number of animal experiments with different strains.

F. Eschbaum (1918) and J. Traube (1920) were the first to attempt an explanation of these phenomena on a physico-chemical basis. Traube (1920) found that 0.1 per cent solutions of the hydrocupreines show a decrease of the surface tension corresponding to their molecular weights. When the alkalinity of these solutions is changed by the addition of varying quantities of sodium bicarbonate this decrease of the surface tension occurs more rapidly; with isooctylhydrocupreine it reaches its minimum and goes up with the higher homologs. Similar results were obtained with ethyl, isoamyl, and isooctylhydrocupreinotoxine, and in both series surface tension and bactericidal action are closely parallel.

In another series of experiments Traube studied the surface-tension of ethyl, isoamyl and isooctylhydrocupreine in different concentrations with the addition of different quantities of sodium bicarbonate.

Chart 6 illustrates these experiments. It shows that corresponding to the decreasing concentration the surface tension goes up and that the clear solutions become more or less opalescent, indicating that the alkalinity affects the surface tension and that a change from the crystalloidal to the colloidal phase takes place. It may, however, be pointed out that with isoamylhydrocupreine dihydrochloride the change for the addition of 0.4 cc. of a 0.2 per cent solution of sodium carbonate occurs differently in that the surface tension decreases with the higher dilutions up to 0.05 per cent; and in concentrations of 0.005 per cent it is still lower than that of the 0.1 per cent solutions.

It appears, therefore, that in addition to the chemical structure, the surface tension, the solubility of the compounds, the pH of the solutions and the dispersion of the particles are involved in the antiseptic action.

In this connection the experiments of Lipschitz and Freund (1923) may be mentioned. They studied the effect of quinine and hydrocupreines on the oxygen metabolism of muscle cells of frogs and guinea pigs and of *Staphylococcus albus* and of streptococcus (Lipschitz, 1923).

They found that the muscle cells are much less affected by the higher homologs, the efficiency increasing from quinine 1 to isooctylhydrocupreine 5, which is in contrast to their toxicity for *Staphylococcus albus* and streptococcus. With *Staphylococcus albus* it ranges from 1 for quinine to 40 for isooctylhydrocupreine and for streptococcus from 1 to 75. The higher homologs combine, therefore, a greater toxicity for bacteria with a comparatively weak effect on the muscle cell. It is interesting that eucupinotoxine shows a lower toxicity for muscle cells and a greater efficiency against bacteria, which may explain the observation of Morgenroth and Bumke (1918) that eucupinotoxine is a more prompt and more powerful antiseptic than eucupine itself. The fact that the larger cells are less affected than the microorganisms and that substances such as eucupine and vuzine which lower the surface tension more markedly and therefore which are more surface-active, are more effective in affecting the vital functions of smaller cells, seems to indicate that surface phenomena are involved in this effect.

Braun and Schaeffer (1917) had already emphasized that the aliphatic alcohols show the same phenomenon as the hydrocupreines, since their antiseptic action increases with the molecular

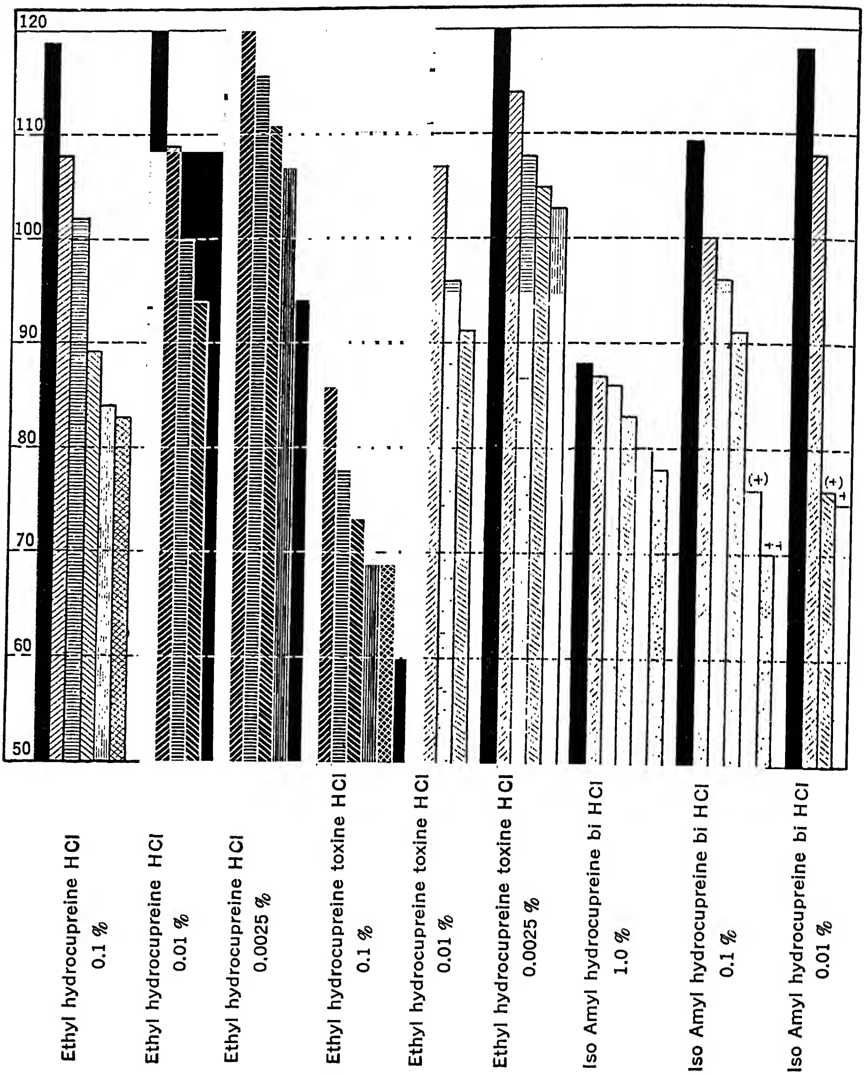


CHART 6. See caption on right-hand page.

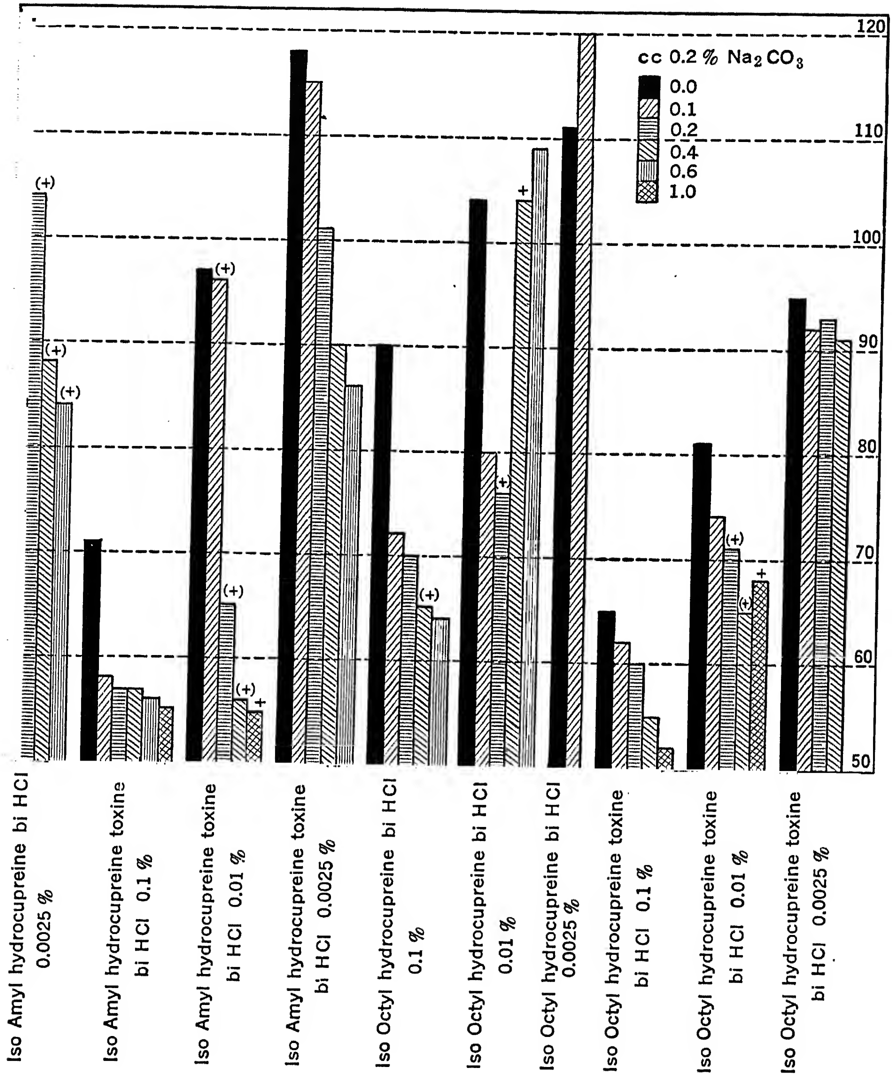


CHART 6.—Effect of Alkali on the Surface Tension of Hydrocupreines in Various Concentrations. (J. Traube)

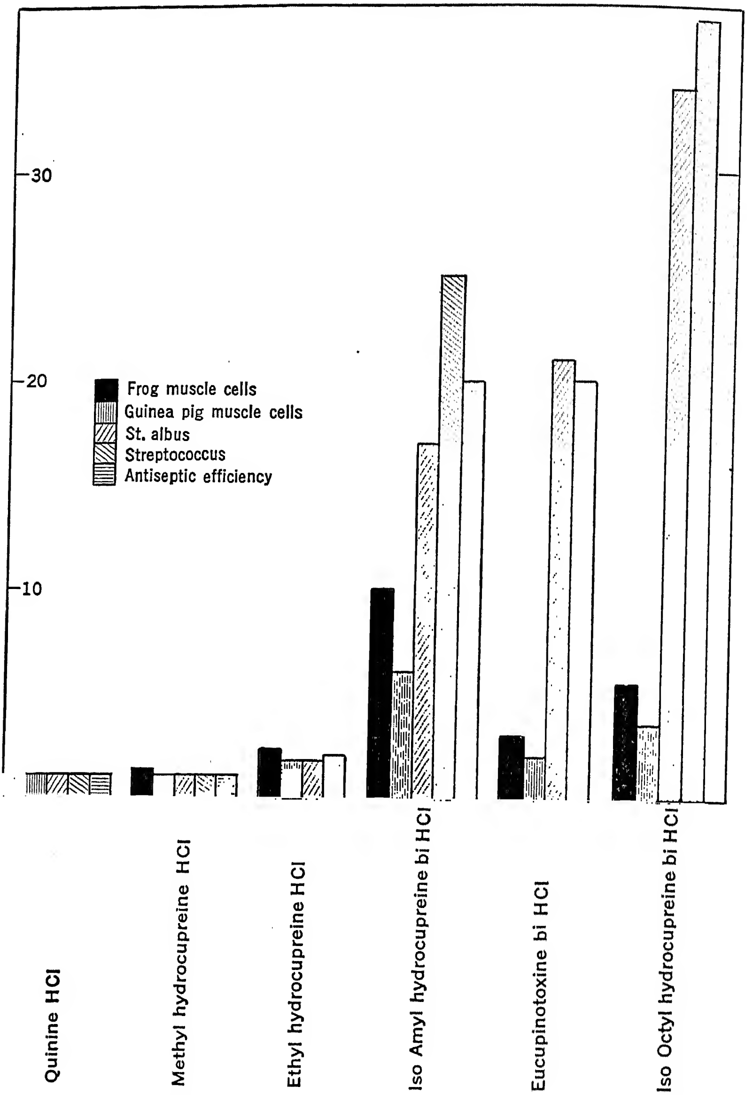


CHART 7.— Effect of Hydrocupreines on the Oxygen Metabolism of Muscle Cells and Bacteria. (Lipschitz and Freund)

The unit is the degree of efficiency of the different hydrocupreines compared with quinine, that of the latter being one.

weight. They confirmed the work previously reported by Saul (1898), Stadler (1911) and Wirgin (1904). It may be seen from Table 14, which is based on the results of Rikl (1928)

and Wirgin (1904), that this parallelism concerns not only the antiseptic action but also the irritation of the nerve-endings and the hemolytic action.

TABLE 14.—*Chemical Constitution and Pharmacologic Action of Aliphatic Alcohols.*

Compound	Local Irritation Mol. per Liter (Rikl)		Antiseptic Action *M. pyogenes aureus* (Wirgin)	Hemolytic Action in Per Cent Solution
	Eye	Tongue		
Methyl alcohol	0.624	7.805	9:100	11.6
Ethyl alcohol	0.217	3.472	7:100	9.82
Propyl alcohol	0.083	1.665	4:100	4.6
Iso propyl alcohol..	0.168	4.163	4:100	4.6
Butyl alcohol	0.034	0.337	3:100	2.3
Iso butyl alcohol ...	0.067	0.675	3:100	2.3
Tert. butyl alcohol..	0.135	4.050	5:100	...
Iso amyl alcohol ...	0.014	0.226	1:100	2.3
Tert. amyl alcohol..	0.034	0.687	3:100	0.6
Heptyl alcohol	0.002	0.009	....	...

Since the compounds in Table 14 are soluble in water, at least to the extent used in these experiments, and these studies are not complicated by changes of the pH or of the dispersion, it appears that the molecular weight is involved in this phenomenon, and that irritation, antiseptic and hemolytic action follow the same direction rather closely.

With the hydrocupreine derivatives, however, a second factor comes in, namely the solubility of these bases in aqueous solutions. While the salts are freely soluble in water, the free bases are only slightly soluble; the solubility decreasing with the higher homologs. Michaelis and Dernby (1922) studied the solubilities of isoamyl and isooctylhydrocupreine and of isoamylhydrocupreinotoxine and found that these vary with different pH. Chart 8 is plotted from their data and shows that the solubility of these compounds varies in inverse ratio to the pH.

If it is assumed that the pH of the tissue is about 7.4, it may be seen from the diagram that at this pH considerably larger quantities of the isoamyl compound are dissolved than of the isooctyl compound as well as of the isoamylhydrocupreinotoxine. But since the isooctyl compound is generally the more potent, it becomes evident that the solubility as such is not the determining factor in the toxic action.

Michaelis and Dernby (1922) studied further the relation between surface tension and pH.

They found (Chart 9) that the surface tension of the isoamylhydrocupreine decreases gradually with the pH up to pH 6.8, after which the surface tension increases with the pH. The concentrations used in these experiments were 1 : 10,000 and 3 : 10,000 and as may be seen from Chart 8 isoamylhydrocupreine is soluble at pH 6.8 to the extent of 6 : 10,000, so that the change

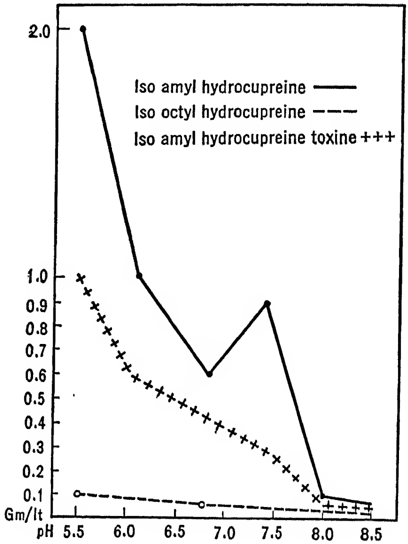


CHART 8.—Solubility of Iso-Amyl and Iso-Octylhydrocupreine and of Iso-Amylhydrocupreino-toxine at Different pH. (Michaelis and Dernby)

of the surface tension cannot be explained on the base of a change from the crystalloid to the colloid phase.

Michaelis and Dernby (1922) further studied the effect of the hydrogen-ion concentration on the disinfectant action of isoamylhydrocupreine. Chart 10 shows that the optimal effect is obtained at pH 8.0, i.e., at a point where the solubility is considerably reduced and the surface tension is still markedly decreased (3 : 10,000) or becomes zero (1 : 10,000). This effect of the pH on the disinfectant action of hydrocupreine solutions also explains the phenomenon observed by Braun and Schaeffer, that the dihydrochlorides are less effective than the corresponding monohydrochlorides.

From these data it becomes evident that there is no satisfactory explanation for the mechanism of action of hydrocupreines and that the changes of the surface tension depend very much on the

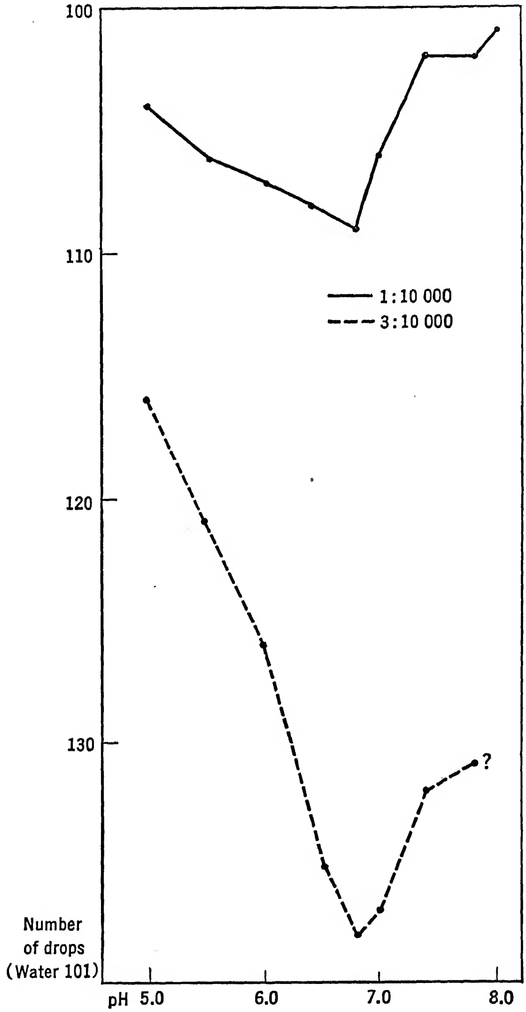


CHART 9.—Relation between pH, Concentration, and Surface Tension of Iso-Amylhydrocupreine. (Michaelis and Dernby)

concentrations of the alkaloids and on the pH. It is difficult, if not impossible, to predict in which direction the changes may occur in the organism.

The question arises, therefore, whether a colloidal phenomenon may not also be involved in the antiseptic action, perhaps in a manner similar to that assumed by Langer (1922) for the antiseptic action of certain dyes. This theory will be discussed later. From these data it becomes evident, however, that at the pH of normal tissue and especially at that of inflamed tissue, the iso-

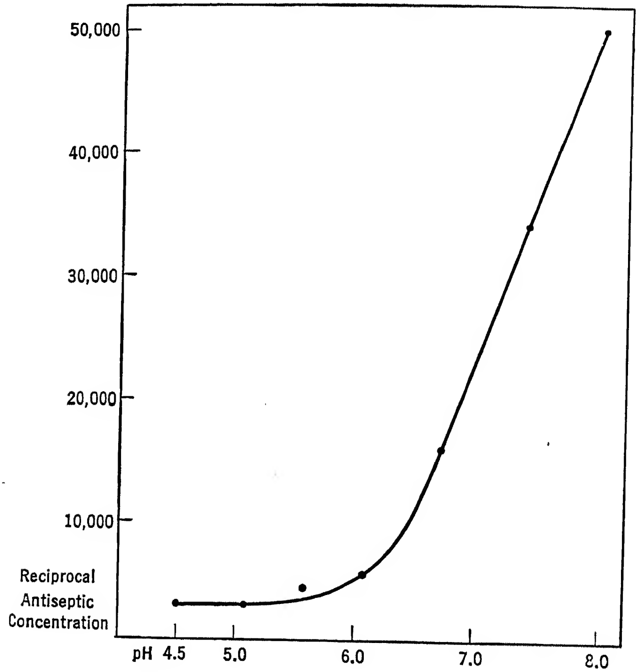


Chart 10.—Effect of pH on the Antiseptic Concentration of Iso-Amylhydrocupreine for *Staphylococcus aureus*. (Michaelis and Dernby)

octylhydrocupreine cannot develop its maximal disinfectant power, and that differences in the clinical results may be explained at least in part on this basis. Traube stated that with the exception of meningococci and gonococci, all bacteria for which the dependence of the disinfectant action of hydrocupreines on the surface tension was established, are gram positive, and according to Eisenberg (1913) these are also more intensively and more rapidly stained than other bacteria.

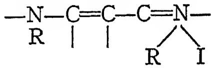
Chapter X.

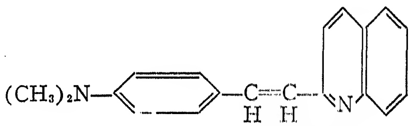
Quinoline Dyes.

Another group of quinoline derivatives which has been studied in regard to the relation between chemical constitution and pharmacologic action are the quinoline dyes. In the older literature **quinoline blue** or **cyanine,** a dye containing the group $C_{19}H_{13}N_2$ and **quinoline red** ($C_6H_5(C_9H_6NCH_2)C = C_9H_6NCl$) are of some interest. According to Behring (**1889**) the former is a good bactericide, and Tagami (**1932**) reported that the bactericidal action is not influenced by the pH. Tappeiner and Jodlbauer (**1895**) determined the minimal concentration which killed paramecia in from 30 to 60 hours as 1:100,000, concentrations of 1:500,000 being non-toxic. Martinotti (**1888**) found it very toxic for tadpoles and Galeotti (**1894**) stated that intraperitoneal injection of 2 cc. of a saturated solution into salamanders was fatal within from five to six hours. In regard to certain theories which will be discussed later we should mention the statement of Ehrlich (**1887**) that mixtures of alcoholic solutions of the dye with normal saline do not stain the central nervous system *in vivo,* while the solution mixed with serum instead of saline produces vital staining. In the latter instance the dye apparently enters the circulation in a state of greater subdivision and therefore can pass the choroid plexus. Tappeiner and Jodlbauer (**1897**) found quinoline red less toxic in the dark than in the light and as a whole less toxic than cyanine.

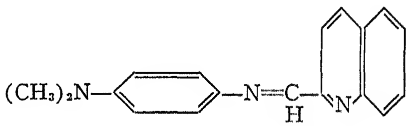
It has been shown that quinoline and some of its derivatives have *antiseptic properties* but these are not very marked and Browning and his co-workers (**1922**) pointed out that **quinoline hydrochloride, tetrahydroquinoline hydrochloride, 8-aminoquinoline hydrochloride, 7-aminoquinoline hydrochloride, 6-aminoquinoline and 5-aminoquinoline hydrochloride** all fail to sterilize solutions if the dilution exceeds 1:200 either in aqueous solution of peptone or in serum. The methochlorides of these compounds with the exception of that of the 8-derivative show an increased antiseptic action as compared with the corre-

sponding unsubstituted compounds. The hydrochlorides of the α- and β-naphtholquinolines were found to be slightly more effective, but there is no striking difference between these and their tetrahydro derivatives. Also diamino-α-naphtholquinoline shows no greater activity, while the methochlorides of both develop a more marked bactericidal action in serum.

More recently Browning and his co-workers (1924) made an extensive study of the antiseptic action of quinoline dyes. They assumed that a chain of alternating double linkage joining the nitrogen atom, one being of basic nature and trivalent, the other being pentavalent, of the following type was important:
. Such a structure is present in acriflavine and cyanine and may be essential for the antiseptic action analogous to the assumption of Pope that such groups are necessary for the photosensitizing action. Such a system is present with the styrol compounds, while an additional nitrogen atom is interposed in the connecting chain in the anil quinoline derivatives.



2-(p-dimethylamino)styrylquinoline



2-(p-dimethylamino)anilquinoline

Browning found that both the p-aminostyrylquinoline methochloride and the p-aminoanilquinoline methochloride are moderately antiseptic against *Staphylococcus aureus* but ineffective against *Bacillus coli.* He studied the effect of substitutions in the benzene ring, in the primary amino group, in the tertiary amino group, and that of substitution in the quinoline ring by primary amino groups, tertiary amino groups, acetyl amino groups and acetic groups. He also studied the effect of sulfonation and that of a change to an azo group; and the effect of changes of the position of the styryl and anil complex in regard to the quino-

line group, and that of the change of the quinoline nitrogen to a quaternary base.

Substitution in the benzene ring (2-styryl-6-methylquinoline methochloride). This compound is very sparingly soluble in water, and results of experiments on the antiseptic action are therefore not very reliable, but its potency in serum is distinctly less than that of the corresponding aminostyryl compound and considerably below that of the dimethylaminostyryl-6-methylquinoline methochloride. The corresponding anil derivative is markedly antiseptic for *Staphylococcus aureus* in aqueous solution but has only very little effect in the presence of serum; in both media it is distinctly less effective against *Bacillus coli.*

Primary amino groups. Introduction of a primary amino group in the benzene ring has only a moderate effect on the antiseptic action against *Staphylococcus aureus* and *Bacillus coli,* the para compound being more potent than the ortho and meta compounds (1,2,3), both interfering with the alternating linkage system.

Tertiary amino group. Methylation of the amino group in para position of the styryl and anil compound increases the antiseptic action (14-1; 16-4; 21-6; 23-7; 27-9; 37-11; 47-4; 48-42; 56-43; 59-45; 75-46), but this change has very little effect on the trypanocidal action of these compounds.

Acetylation. Acetylation of the amino group of the benzene ring reduces the antiseptic action (1-86; 6-87; 11-90) and all these compounds are characterized by the absence of the basic group from the alternating linkage chain. These substances are, however, frequently less toxic for the host and have also a higher trypanocidal value (1-86).

Sheehan (1932) studied 2-(p-acetylaminostyryl)-6-dimethylamino-quinoline methochloride as to its behavior in rabbits and found that it has considerably nephrotoxic properties.

Browning, Cohen, Cooper, and Gulbranson (1932) studied the trypanocidal effect of a series of compounds in which both amino groups were substituted by acid radicles (Table 16). They found that the introduction of a lactyl group into the aminostyryl radicle (Table 16, 391) had practically the same curative value as 2-(p-aminostyryl)-6-acetylamino-quinoline methochloride (Table 15, 8) and that the acetylation of the amino group (Table 16, 397) did not materially alter the efficiency, but it was noticed that

TABLE 15.—*Relation between Chemical Constitution and Antiseptic Action of Anil and Styryl Quinoline Derivatives.*
(Browning, *et al.*)

No.	Compound	*Staphylococcus aureus* Peptone Water +	±	−	Serum +	±	−	*B. coli* Peptone Water +	±	−	Serum +	±	−	Precipitate P	S	*Trypanosoma Brucei* Dose	Result
1	p$NH_2\overset{2}{St}Q$(MeCl)	100	40	20	40	...	20	10	4	2	40	20	10	...	...	1:4000	Slight
2	o$NH_2\overset{2}{St}6CH_3Q$(MeCl)	40	10	4	2	...	?	4	2	?	4	2	?	2	...	...	...
3	m$NH_2\overset{2}{St}6CH_3Q$(MeCl)	40	10	4	20	10	4	10	4	1	20	10	4	...	...	...	...
4	p$NH_2\overset{2}{St}6CH_3Q$(MeCl)	100	...	40	100	40	20	20	10	1	40	20	10	4	...	...	...
5	p$NH_2\overset{2}{St}\beta$-naphthoQ(MeCl)	400	200	100	200	...	100	2	...	?	200	100	40	10	2	...	...
6	p$NH_2\overset{2}{St}6NH_2Q$(MeCl)	200	100	40	200	...	100	40	20	4	200	100	20	...	...	...	...
7	p$NH_2\overset{2}{St}6NHCOCH_3Q$(HCl)	4	2	?	2	...	?	2	...	?	2	...	?	20	8	1:6000 1:7500	Cure Marked
8	p$NH_2\overset{2}{St}6NHCOCH_3Q$(MeCl)	2	1	?	40	20	4	1	...	?	1	...	?	10	10	...	...
9	p$NH_2\overset{2}{St}6NHCOC_2H_5Q$(MeCl)	40	20	?	100	40	20	1	...	?	20	10	4	10	4	1:600 1:4000	Cure
10	p$NH_2\overset{2}{St}7NHCOCH_3Q$(MeCl)	40	20	?	100	40	20	1	...	?	20	...	10	4	...	1:2000 1:5000	Cure
11	p$NH_2\overset{2}{St}6N(CH_3)2Q$(MeCl)	400	200	100	400	200	100	10	...	4	200	...	100	...	...	1:2000 1:5000 1:20 000	Cure 0 0

Explanation: In this table + indicates free growth of the organisms with development of marked turbidity in the medium; ± inhibition of growth, medium only faintly turbid or remaining unclouded, but in the latter case subcultures yielded growth; — complete sterility. The figures are the reciprocals of the dilutions which produce the effect indicated divided by one thousand. Under precipitation, the figures similarly converted, record the highest dilution within the range investigated at which precipitation occurs; — means absence of precipitation. In the column Tryp. Brucei the figures give the concentrations of which 1 cc. per 20 Gm. mouse infected with Tryp. Brucei had the following effects: "trace" prolongation of life for several days beyond that of the untreated controls; "slight" prolongation of life for several days and disappearance of the parasites from the blood for several days or a week; "marked" absence of parasites for ten days or longer; "(cure)" cure effected only in a proportion of the animals treated; "cure" complete cure.

12	pNH$_2\overset{2}{\mathrm{S}}$t6NHCOCH$_3$Q(MeCl) sulfonate	400	200	40	200	100	40	200	100	10	400	200	40	...	...	...	...
13	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$tP(MeI)	100	...	40	100	...	40	20	10	4	100	40	20	...	...	...	...
14	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$tQ(MeCl)	200	...	100	200	...	100	20	...	10	100	...	40	...	...	1 : 12 000	0
15	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$tQ(MeI)	1000	400	200	1000	...	400	1000	...	40	400	200	40	...	...	1 : 6000	0
16	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6(CH$_3$)Q(MeCl)	2000	...	1000	2000	1000	400	200	...	100	400	200	100	...	...	1 : 12 000	0
17	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6β-naphthoQ(MeCl)	1000	...	400	400	...	200	200	100	20	100	40	20	10	...	1 : 500	0
18	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6OCH$_3$Q(MeI)	2000	400	200	1000	...	400	200	100	40	200	...	100	...	...	...	...
19	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6OC$_2$H$_5$Q(MeI)	4000	2000	1000	2000	1000	400	400	100	20	1000	400	100	...	...	...	...
20	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6-7$\overset{\circ}{8}$ CH$_2$Q(MeS)	200	100	20	200	...	100	40	4	?	200	...	100	...	...	1 : 6000	0
21	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6NH$_2$Q(MeCl)	400	200	100	400	200	100	200	100	20	400	200	40	...	...	1 : 6000	Slight
21a	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6NH$_2$QHCl	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1 : 6000	Slight
21b	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6NH$_2$Q(MeCl)HCl	...	...	...	...	...	...	...	...	...	...	...	...	...	...	{1 : 1000 {1 : 2000	Cure (Cure)
22	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6NHCOHQ(MeCl)	100	40	?	200	100	40	1	...	?	40	20	1	40	...	1 : 2500	Cure
22a	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6NHCOHQ(MeI)	...	...	...	...	...	...	...	...	...	...	...	...	...	...	{1 : 2000 {1 : 1200	Cure Cure
23	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6NHCOCH$_3$QHCl	10	4	?	4	...	?	1	...	?	1	...	?	10	10	...	...
24	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6NHCOCH$_3$Q(MeCl)	400	200	40	200	100	40	1	...	?	100	40	20	20	...	{1 : 750— {1 : 4000	Cure Cure
24a	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6NHCOCH$_3$Q(MeBr)	...	...	...	...	...	...	...	...	...	...	...	...	...	...	{1 : 1000— {1 : 3000	Cure Cure
24b	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6NHCOCH$_3$Q(MeI)	...	...	...	...	...	...	...	...	...	...	...	...	...	...	{1 : 500— {1 : 6000	Cure Cure
25	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6NHCOCH$_3$Q(MeS)	100	40	?	100	40	20	2	...	?	100	...	40	10	...	{1 : 750— {1 : 7500	Cure Cure
26	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6NHCOCH$_3$Q(EtS)	100	40	10	100	40	20	1	...	?	40	20	10	10	...	1 : 1200	Slight
27	p(CH$_3$)$_2$N$\overset{2}{\mathrm{S}}$t6NHCOC$_2$H$_5$Q(MeCl)	1000	400	200	400	...	200	20	10	?	400	200	40	20	..	{1 : 2000 {1 : 5000	Cure Slight

TABLE 15—*Continued*

No.	Compound	*Staphylococcus aureus*						*B. coli*						Precipitate		*Trypanosoma Brucei*	
		Peptone Water			Serum			Peptone Water			Serum						
		+	±	−	+	±	−	+	±	−	+	±	−	P	S	Dose	Result
28	$p(CH_3)_2N\overset{2}{S}t6NHCOC_3H_7Q(MeCl)$	1000	400	200	400	...	200	100	40	4	400	200	100	4	...	{1 : 1000 {1 : 1200	Cure Marked
29	$p(CH_3)_2N\overset{2}{S}t6NHCOC_4H_9Q(MeCl)$	1000	...	400	400	200	100	40	20	10	400	200	100	10	1	{1 : 3000 {1 : 10 000	Cure 0
30	$p(CH_3)_2N\overset{2}{S}t6NHCOC_5H_{11}Q(MeCl)$	?	1000	200	1000	...	400	20	...	10	200	...	100	10	...	{1 : 1500 {1 : 10 000	Cure 0
31	$p(CH_3)_2N\overset{2}{S}t6NHCOCH(C_2H_5)_2Q$ (MeCl)	1000	400	100	400	200	100	1	...	?	100	...	40	10	...	{1 : 1500 {1 : 10 000	Cure 0
32	$p(CH_3)_2N\overset{2}{S}t6NHCOCBr(C_2H_5)_2Q$ (MeCl)	4000	...	1000	1000	400	200	100	40	2	100	...	40	10	4	1 : 1000	Marked
33	$p(CH_3)_2N\overset{2}{S}t6NHCOCH_2ClQ(MeCl)$	400	200	10	40	20	10	2	...	?	40	...	20	10	4	1 : 400	Marked
34	$p(CH_3)_2N\overset{2}{S}t6NHCOCH_2BrQ(MeCl)$	400	200	8	40	20	10	2	...	?	40	20	2	8	...	1 : 750	0
35	$p(CH_3)_2N\overset{2}{S}t6NHCOCCl_3Q(MeCl)$	400	200	40	200	100	40	1	...	?	100	40	20	10	...	1 : 150	0
36	$p(CH_3)_2N\overset{2}{S}t7NHCOCH_3Q(MeS)$	100	40	2	200	100	40	1	...	?	100	40	20	10	2	1 : 2500	Slight
37	$p(CH_3)_2N\overset{2}{S}t6N(CH_3)_2Q(MeCl)$	2000	1000	400	400	200	100	1000	...	400	400	...	200	...	...	1 : 8000	0
38	$p(CH_3)_2N\overset{2}{S}t6N{:}NH(acid)Q(MeCl)$	4	2	?	10	4	?	1	...	?	1	...	?	20	...	1 : 100	0
39	$p(CH_3)_2N\overset{2}{S}t6NHCOCH_3Q(MeCl)$ sulf.	1000	400	100	1000	400	200	400	200	40	400	200	100	...	...	...	...
40	$p(CH_3)_2N\overset{4}{S}t6CH_3Q(MeCl)$	400	200	40	200	100	40	40	...	20	40	...	20	...	...	1 : 12 000	0
41	$pNH_2\overset{2}{A}Q(MeCl)$	100	40	20	40	...	20	40	20	4	100	40	10	...	...	...	...
42	$pNH_2\overset{2}{A}6CH_3Q(MeCl)$	200	100	40	200	100	40	100	40	20	100	...	40	...	...	...	...
43	$pNH_2\overset{2}{A}6NH_2Q(MeCl)$	40	20	10	40	20	10	40	20	4	40	20	4	...	...	...	...

44	$pNH_2\overset{2}{A}7NH_2Q$ (MeCl)	100	...	40	100	...	40	20	10	4	40	20	10	...	...	...	...
45	$pNH_2\overset{2}{A}6NHCOCH_3Q$ (MeCl)	40	20	10	40	...	20	40	20	10	200	100	40	...	...	...	...
46	$pNH_2\overset{2}{A}6N(CH_3)_2Q$ (MeCl)	100	...	40	200	...	100	40	20	4	200	100	40	...	...	...	...
47	$p(CH_3)_2N\overset{2}{A}Q$ (MeCl)	400	200	100	400	200	100	400	200	100	?	1000	200	...	...	...	...
48	$p(CH_3)_2N\overset{2}{A}6CH_3Q$ (MeCl)	1000	400	200	1000	400	200	1000	400	200	1000	400	200	...	...	...	...
49	$p(C_2H_5)_2N\overset{2}{A}6CH_3Q$ (MeCl)	1000	...	400	1000	400	100	400	...	200	200	...	100	...	...	...	...
50	$p(C_2H_5)_2N\overset{2}{A}6CH_3Q$ (MeI)	1000	400	100	400	200	100	100	...	40	200	100	40	...	...	...	...
51	$p(CH_3)_2N\overset{2}{A}6CH_38CH_3Q$ (MeCl)	400	...	200	100	40	20	400	...	200	200	...	100	...	...	...	...
52	$p(CH_3)_2N\overset{2}{A}\beta$-naphtho$Q$ (MeCl)	?	4000	2000	2000	1000	400	?	2000	400	?	2000	400	...	...	...	...
53	$p(CH_3)_2N\overset{2}{A}6OCH_3Q$ (MeCl)	2000	1000	200	200	...	100	200	100	40	1000	400	100	...	...	...	...
54	$p(CH_3)_2N\overset{2}{A}6OC_2H_5Q$ (MeCl)	1000	...	400	1000	...	400	400	...	200	2000	1000	200	...	...	...	...
55	$p(CH_3)_2N\overset{2}{A}6\text{-}7\overset{8}{C}H_2Q$ (MeS)	100	40	20	200	...	100	40	20	10	400	200	100	2	...	...	...
56	$p(CH_3)_2N\overset{2}{A}6NH_2Q$ (MeCl)	400	...	200	400	200	100	200	...	100	400	200	100	...	...	...	...
57	$p(CH_3)_2N\overset{2}{A}6NH_2Q$ (MeI)	40	20	10	40	20	10	20	...	10	100	40	10	...	...	...	...
58	$p(CH_3)_2N\overset{2}{A}6NHCOHQ$ (MeCl)	100	40	20	100	...	40	100	...	40	400	200	100	...	...	...	...
59	$p(CH_3)_2N\overset{2}{A}6NHCOCH_3Q$ (MeCl)	2000	1000	400	400	...	200	1000	...	400	2000	1000	400	...	...	...	...
60	$p(CH_3)_2N\overset{2}{A}6NHCOCH_3Q$ (MeBr) ...	?	1000	200	400	200	100	1000	...	400	?	1000	400	...	...	...	...
61	$p(CH_3)_2N\overset{2}{A}6NHCOCH_3Q$ (MeI)	1000	400	200	1000	400	200	1000	400	40	?	...	1000	...	...	...	...
62	$p(CH_3)_2N\overset{2}{A}6NHCOCH_3Q$ (MeS)	1000	...	400	400	200	40	400	...	200	?	1000	400	...	...	...	...
63	$p(CH_3)_2N\overset{2}{A}6NHCOCH_3Q$ (EtS)	?	1000	200	1000	400	200	200	100	40	1000	400	200	...	...	...	...
64	$p(C_2H_5)_2N\overset{2}{A}6NHCOCH_3Q$ (MeCl) ...	?	1000	400	1000	400	200	400	200	100	1000	400	200	...	...	...	...
65	$p(CH_3)_2N\overset{2}{A}6NHCOC_2H_5Q$ (MeCl) ...	?	?	1000	1000	400	200	?	1000	200	?	?	1000	...	...	...	...

TABLE 15—*Continued*

No.	Compound	*Staphylococcus aureus* Peptone Water +	±	−	Serum +	±	−	*B. coli* Peptone Water +	±	−	Serum +	±	−	Precipitate P	S	*Trypanosoma Brucei* Dose	Result
66	$p(CH_3)_2N\overset{2}{A}6NHCOC_3H_7Q(MeCl)$ ...	1000	400	200	200	100	40	400	...	200	?	4000	400	...	...	...	...
67	$p(CH_3)_2N\overset{2}{A}6NHCOC_4H_9Q(MeCl)$ ...	1000	...	400	1000	400	200	4000	1000	400	2000	1000	400	...	...	...	...
68	$p(CH_3)_2N\overset{2}{A}6NHCOC_5H_{11}Q(MeCl)$ ...	10 000	4000	1000	1000	400	200	4000	2000	1000	4000	2000	400	10	...	...	...
69	$p(CH_3)_2N\overset{2}{A}6NHCOCH(C_2H_5)_2Q$ (MeCl)	?	1000	400	?	1000	200	4000	2000	400	2000	1000	400	...	...	...	...
70	$p(CH_3)_2N\overset{2}{A}6NHCOCBr(C_2H_5)_2Q$ (MeCl)	?	?	1000	400	200	100	1000	400	100	1000	400	40	...	...	...	...
71	$p(CH_3)_2N\overset{2}{A}6NHCOCH_2ClQ(MeCl)$ ..	1000	400	200	200	100	40	1000	400	200	400	200	100	...	...	...	...
72	$p(CH_3)_2N\overset{2}{A}6NHCOCH_2BrQ(MeCl)$.	400	...	200	100	40	10	100	...	40	400	200	100	...	...	...	...
73	$p(CH_3)_2N\overset{2}{A}6NHCOC_6H_5Q(MeAc)$ ...	200	...	100	40	20	4	400	...	200	400	200	100	...	...	...	...
74	$p(CH_3)_2N\overset{2}{A}7NHCOCH_3Q(MeCl)$	2000	1000	400	2000	1000	400	400	200	100	1000	400	200	...	...	...	...
75	$p(CH_3)_2N\overset{2}{A}6N(CH_3)_2Q(MeCl)$	1000	400	200	400	200	100	100	...	40	400	...	200	...	...	...	...
76	$p(CH_3)_2N\overset{2}{A}6N(CH_3)_2Q(MeI)$	1000	...	400	400	200	100	200	...	100	200	...	100	...	...	...	...
77	$p(CH_3)_2N\overset{2}{A}6ClQ(MeCl)$	400	200	100	200	...	100	200	...	100	200	...	100	...	...	...	...
78	$p(CH_3)_2N\overset{2}{A}6BrQ(MeCl)$	200	100	40	20	...	10	40	20	10	40	20	4	...	...	...	...
79	$p(CH_3)_2N\overset{2}{A}6NO_2Q(MeCl)$	100	...	40	20	10	4	200	100	4	10	...	4	10	4	...	...
80	$p(CH_3)_2N\overset{2}{A}6N{:}NH(acid)Q(MeCl)$ ..	1	...	?	1	...	?	1	...	?	1	...	?	200	...	...	...
81	$p(CH_3)_2N\overset{3}{A}6NHCOCH_3Q(MeCl)$ sulf.	1000	400	200	1000	400	200	400	200	100	?	1000	200	...	...	...	...
82	$p(CH_3)_2\overset{4}{A}6CH_3Q(MeCl)$	100	...	40	100	40	20	10	...	4	10	...	4	...	...	...	...

83	2St6CH_3Q(MeCl)	200	100	40	20	10	4	2	...	1	10	...	4	4	...	...	...
84	mOHpOH2StQ(MeS)	20	4	2	4	2	1	1	?	?	2	...	1	10	2	...	...
85	mp$\overset{O}{O}CH_2$2StQ(MeS)	40	20	10	10	4	2	1	...	?	20	...	10	1	...	...	...
86	pCH_3CONH2StQ(MeCl)	20	10	4	20	...	10	1	...	?	20	...	10	1	...	1 : 15 000	Trace
87	pCH_3CONH2St6NH_2Q(MeCl)	2	...	?	20	10	4	1	...	?	1	...	?	100	4	{1 : 5000— {1 : 7500	Cure Cure
88	pCH_3CONH2St6NHCOCH_3Q(MeCl) .	2	...	?	2	...	?	2	...	?	2	...	?	100	10	1 : 1500	Cure
89	pCH_3CONH2St6NHCOCH_3Q(MeS) .	1	...	?	1	...	?	1	...	?	1	...	?	100	20	...	...
90	pCH_3CONH2St6N$(CH_3)_2$Q(MeCl) ..	40	20	1	100	...	40	1	...	?	10	...	4	...	...	{1 : 750— {1 : 4000	Cure Cure
91	2A6CH_3Q(MeCl)	200	...	100	20	...	10	1	...	?	2	...	1	...	...	...	...
92	2A6NHCOCH_3Q(MeCl)	1	...	?	2	...	1	1	...	?	1	...	?	...	...	...	...
93	2A6N$(CH_3)_2$Q(MeCl)	40	20	10	200	100	20	20	4	2	400	200	100	...	...	...	...
94	pCH_3CONH2A6NHCOCH_3Q(MeCl) .	2	...	1	2	...	1	2	...	1	2	...	1	...	...	...	...

the latter compound has convulsant action which is even more marked with 2-(p-acetylaminostyryl)-6-glycerylaminoquinoline methochloride (Table 16, 417).

Substitution in the quinoline ring. Introduction of a second cyclic nucleus into the quinoline ring with the formation of β-naphtholquinoline derivatives slightly increases the antiseptic action in the case of the styryl compounds (5-1; 17-14). The corresponding anil derivative (52) shows a marked increase as compared with p-dimethylaminoanilquinoline methochloride (41) and it is exceedingly effective against *Staphylococcus aureus* and *Bacillus coli* both in peptone water and in serum. On the other hand, the pyridine derivative (13) of similar structure as (14) is a weaker antiseptic than the latter.

In the dimethylaminostyryl series the *introduction of methyl and ethoxy groups* in position 6- increases the antiseptic action especially against staphylococci, but the methoxy group seems to be less effective than the ethoxy group (16, 19, 18). The corresponding anil derivatives (48, 51, 53 and 54) do not show a distinct increase of efficiency and the same holds true for the p-aminoanil compounds (42-41). The 6,7-methylenedioxide derivatives are somewhat less effective against *Staphylococcus aureus* and *Bacillus coli* (20, 55).

The effect of a *primary amino group* introduced into the quinoline ring has not been definitely determined, but this is not very marked in any case (43, 44-41; 6-1). For the trypanocidal action of these compounds its present seems to be indispensable (Browning, Cohen, Ellingworth and Gulbranson, **1929**); its substitution by methyl groups increases the toxicity (Ehrlich's distherapeutic effect) and only the methochloride is effective.

The antiseptic action is also markedly increased by the *methylation* of the amino group, especially if the primary compound is already fairly active (6-11). The greater solubility of p-acetylaminostyryl-6-dimethylaminoquinoline methochloride may explain its superior efficiency as compared with p-acetylaminostyryl-6-aminoquinoline methochloride.

It has been shown that acetylation of the amino group of the benzene ring lowers the antiseptic action. *Acidulation of the amino group* of the quinoline ring has the opposite effect. Some of the acid substituted derivatives of p-dimethylanil-6-aminoquinoline methochloride are in fact quite powerful antiseptics for

Bacillus coli (56-59; 65; 66; 67; 68) the formyl compound (58) is an exception, being less effective than the primary substance. Similar derivatives of the styryl series (23; 27; 28; 29; 30; 31) show little change in efficiency. Acetylation of the amino group frequently reduces the toxicity for the host and at the same time develops more marked trypanocidal action (21-24; 6-7). This effect is, therefore, similar to that discovered by Ehrlich and his school in the case of aminophenylarsinic acid.

Browning, Cohen, Cooper and Gulbranson (**1932**) synthesized another series of acid substituted 6-aminoquinoline derivatives which are given in Table 16.

It may be seen that the anil derivatives (352, 353, 350, 351, 348, and 360) manifest only moderate trypanocidal action with the use of nearly the maximal tolerated dose. The styryl compounds 359, 361 and 412 effect cure in every case but the range of action of these substances appears to be less than with the corresponding acetyl amino compound (Table 15, 8).

Introduction of more complicated acid radicles may yield a different result. The diethylacetyl compound (70) is more and the monobromo and chloroacetyl derivatives (71; 72) are less effective than the unsubstituted acetyl derivative against bacteria (59). On the other hand, the introduction of the chloroacetyl radicle into the amino group increases the trypanocidal action of these compounds considerably, cure being effected by the maximal tolerated dose. The strongly antiseptic 2-(p-dimethylaminoanil)-6-acetylaminoquinoline methochloride has only slight trypanocidal properties and the equally potent antiseptic p-dimethylaminoanil-β-naphtholquinoline methochloride is not trypanocidal. Similar conditions are found with the anil derivatives (32; 33; 34-23).

Introduction of an acid group into position 6- of the quinoline ring diminishes the efficiency. Chlorine is less effective in this respect (77) than bromine and the nitro group (78; 79); this reduction is especially marked when tested in serum. This is in accordance with the observations made with the halogen-substituted acetyl derivatives. Sulfonation renders the substance more soluble in general and, therefore, usually yields more active compounds (12-10; 39-23; 81-59).

Azo dyestuffs of anil and styrylquinoline derivatives show practically no antiseptic action (38; 80).

Changes of the position of the anil and styryl group in regard

TABLE 16.—*Trypanocidal Action of Anil and Styryl Acylaminoquinoline Derivatives.*

(Browning, Cohen, Cooper and Gulbranson, 1932)

No.	Substance	Dose	Result
352	2(p-Dimethylaminoanil)-6-undecylenylamino-quinoline methochloride	1:1000	Slight
353	2(p-Dimethylaminoanil)-6-laurylaminoquinoline methochloride	1:1000	Slight
350	2(p-Dimethylaminoanil)-6-caprylylaminoquinoline methochloride	1:500	Slight
351	2(p-Dimethylaminoanil)-6-pellagonylamino-quinoline methochloride	1:500	Slight
358	2(p-Dimethylaminoanil)-6-acetyl, lactylamino-quinoline methochloride	1:500	Slight
360	2(p-Dimethylaminoanil)-6-lactylaminoquinoline methochloride	1:100	Marked
359	2(p-Aminostyryl)-6-acetyl, lactylaminoquinoline methochloride	1:1000 } 1:7500 }	Cure
		1:10 000	Marked
361	2(p-Aminostyryl)-6-lactylaminoquinoline methochloride	1:1000	Cure
		1:5000	(Cure)
412	2(p-Aminostyryl)-6-glycerylaminoquinoline methochloride	1:500 } 1:5000 }	Cure
		1:10 000	Marked
391	2(p-Lactylaminostyryl)-6-aminoquinoline methochloride	1:1000 } 1:15 000 }	Cure
		1:20 000	Marked
397	2(p-Lactylaminostyryl)-6-acetylaminoquinoline methochloride	1:700 } 1:7500 }	Cure
		1:10 000	Marked
417	2(p-Acetylaminostyryl)-6-glycerylaminoquinoline methochloride	1:5000– } 1:10 000 }	Cure
		1:15 000	Slight
398	2(p-Aminostyryl)acetyl, lactylaminobenzthiazole methochloride	1:600 } 1:1000 }	Cure
		1:2500	Marked
		1:5000	Slight
392	2(p-Acetyl, lactylaminostyryl)aminobenzthiazole methochloride	1:750	Cure
		1:5000	(Cure)
		1:10 000	Slight

Doses per 20 grams bodyweight mouse.
Largest dose gives approximately maximal tolerated dose.
Terms: cure, slight, etc., have the same meaning as in Table 15.

to the quinoline ring: The 4-(p-dimethylaminostyryl) and the 4-(p-dimethylaminoanil) compounds (lepidine derivatives) are less effective than the 2- substituted substances (quinaldine derivatives). Browning assumed that this is due to a change in the

alternating linkage system; and he pointed out that the anil derivatives are distinctly less effective than the corresponding styryl compounds. This is contrary to the results obtained with 2-styryl and 2-anil series.

Changes to quaternary bases. Comparison of the hydrochlorides and the methochlorides of the same series show that the latter are much more effective (7-8; 23-24) and that there is no great difference between methyl and ethyl quaternary salts of the same base (25-26; 62-63). Variations in the acid radicle, i.e., whether methochloride, iodide, bromide or sulfate are substituted, also do not make a great difference (49-50; 59; 60; 61; 62; 63). There are, however, exceptions as, for instance (56-57), the latter being less effective and less soluble.

The trypanocidal action of the anil quinolines is generally less marked than that of the corresponding styryl derivatives; the latter are, however, also much more toxic for the host. Bramachari (1931) found that **2-(p-dimethylaminostyryl)-quinoline hydrochloride, 2-(p-dimethylaminostyryl)-6-oxy-quinoline, 2-(p-dimethylaminostyryl)-6-ethoxyquinoline, 2-(p-dimethylaminostyryl)-6-methylquinoline methiodide and p-dimethylaminobenzal-6-aminoquinoline** had no effect on paramecia in concentrations of 1:2000.

After Cough and King (1930) had found that the introduction of amido groups in p-aminophenyl arsinic acids changed the inactive carboxylic and sulfonic acid derivatives into trypanocidal compounds, Browning, Cohen, Ashley and Gulbranson (1932) synthesized a series of anil and styryl derivatives containing acylamido groups. (*See* Table 17.)

The trypanocidal properties were studied in mice infected with *T. brucei* and the antiseptic efficiency with *Staphylococcus aureus* and *Bacillus coli.* Table 17 gives a résumé of their results. It shows that only those compounds with the acylamido group in position 6- are therapeutically active. Peculiarly enough in this series the anil derivatives are only slightly inferior to the corresponding styryl compounds (385, 403-410, 409), whereas in the acetylamino quinoline series the anil derivative (Table 15, 25) is distinctly less active than the corresponding styryl compound (Table 15, 62). Further it may be seen that the introduction of the acylamido group in position 6- yields more potent substances than substitution in position 8-, 5-, or 4-, and that ethylamides (419, 420) are more toxic than the unsubstituted or the methylacyl-

TABLE 17.—*Antiseptic and Trypanocidal Action of Anil and Styrylquinoline Carboxylamides.*
(Browning, Cohen, Ashley and Gulbranson, 1932)

No.	Substance	Antiseptic Action				Precipitation		Trypanocidal Action	
		Staph. aureus		*B. coli*					
		Peptone	Serum	Peptone	Serum	Peptone	Serum	Dose	Result
385	2-(p-Dimethylaminoanil) quinoline-6-carboxylamide methochloride	20	4	20	10	10	2	1 : 300-1 : 400 1 : 500-1 : 600 1 : 750-1 : 2500	Cure (Cure) Marked
403	2-(p-Dimethylaminoanil) quinoline-6-carboxymethylamide methochloride	40	100	10	10	4	2	1 : 500-1 : 1000 1 : 2500 1 : 5000	Cure (Cure) Slight trace
419	2-(p-Dimethylaminoanil) quinoline-6-carboxylethylamide methochloride	40	20	<1	20	10	2	1 : 2000 1 : 5000	Slight 0
400	2-(p-Dimethylaminoanil) quinoline-5-carboxylamide methoiodide	10	4	2	4	..	..	1 : 750	0
406	2-(p-Dimethylaminoanil) quinoline-5-carboxymethylamide methochloride	40	10	2	4	..	..	1 : 1000	0
395	2-(p-Dimethylaminoanil) quinoline-4-carboxylamide methochloride	2	4	<1	4	..	..	1 : 600	0
405	2-(p-Dimethylaminoanil) quinoline-4-carboxymethylamide methochloride	4	2	<1	2	2	..	1 : 500	0
414	2-(p-Dimethylaminoanil) quinoline-4-carboxylethylamide methoiodide	2	2	<1	<1	..	..	1 : 1500	0

404	2-(p-Dimethylaminostyryl) quinoline-8-carboxylamide methochloride	2	<1	2	<1	20	4	1 : 100	0
410	2-(p-Dimethylaminostyryl) quinoline-6-carboxylamide methosulphate	<1	20	<1	<1	20	2	1 : 250-1 : 2500 1 : 5000 1 : 10 000	Cure Marked Trace
409	2-(p-Dimethylaminostyryl) quinoline-6-carboxymethylamide methosulphate ...	20	20	<1	4	4	2	1 : 500-1 : 5000 1 : 10 000	Cure Marked
420	2-(p-Dimethylaminostyryl) quinoline-6-carboxylethylamide methochloride	100	40	<1	40	10	..	1 : 5000	Slight
401	2-(p-Dimethylaminostyryl) quinoline-5-carboxylamide methoiodide	10	4	<1	4	..	..	1 : 500	Slight
413	2-(p-Dimethylaminostyryl) quinoline-5-carboxymethylamide methochloride ...	400	40	20	40	20	..	1 : 3000	0
393	2-(p-Dimethylaminostyryl) quinoline-4-carboxylamide methoiodide	<3	3	<3	<3	..	..	1 : 800	0
408	2-(p-Dimethylaminostyryl) quinoline-4-carboxymethylamide methochloride ...	1	4	1	<1	10	2	1 : 500	0
418	2-(p-Dimethylaminostyryl) quinoline-4-carboxylethylamide methoiodide	40	1	<1	<1	..	..	1 : 600	0

Antiseptic action: Values represent reciprocals divided by a thousand of those concentrations which produce after 48 hrs. at 37° C. sterility or at least inhibition of growth to such an extent that the medium is only faintly turbid, or when not cloudy yields scanty growth in subcultures.

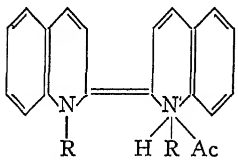
Precipitation: Values represent reciprocals divided by a thousand of the lowest concentration which causes precipitation in the media.

Trypanocidal action: Doses calculated per 20 grams bodyweight of mouse, the highest dose shown for each substance represents the maximal tolerated dose. The terms cure, (cure), etc., indicate the same effects as in the previous tables.

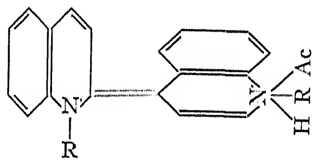
amides (385, 403-410, 409). As to the antiseptic action these substances are not very potent germicides, although some (403, 419, 413, and 420) are quite active.

Browning and his staff (**1924**) studied further some apocyanine, carbocyanine and isocyanine derivatives in regard to their antiseptic action as summarized in Table 18.

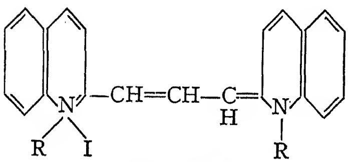
They found that the **erythroapocyanine** compounds (1; 3) are less potent in their antiseptic action against staphylococci than the corresponding **xanthoapocyanines** (2; 4); derivatives of the latter group generally exert a powerful antiseptic action on staphylococci both in aqueous medium and in serum. They are, however, much less effective *in vivo* against *Bacillus coli.* Although there seems to be no marked change of the antiseptic action due to variations of the chemical structure, it is apparent that the amino group tends to diminish rather than to enhance the antiseptic efficiency, in contrast with the experiences in the acridine series.



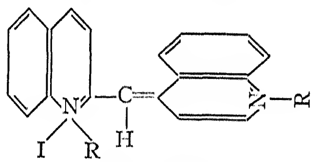
erythroapocyanine



xanthoapocyanine



carbocyanine



isocyanine

The results with **carbocyanine** were so variable that they could not be tabulated in numerical form; Browning attributed the variability to the very slight solubility of these compounds. These compounds are generally powerful antiseptics, killing staphylococci in concentrations of 1:20,000 to 1:200,000 in peptone water and in serum. Most dyes with the exception of the acetate of 1,1′-dimethylcarbocyanine form precipitates in peptone water and concentrations effective against *Bacillus coli* could, therefore, not be obtained. In serum, which holds the dye more readily in solution, the effects are more marked but usually in-

TABLE 18.—*Relation Between Chemical Constitution and Antiseptic Action of Cyanine Derivatives.*
(Browning *et al.*)

No.	Compound	*Staph. aureus*		*B. coli*	
		Peptone wat.	Serum	Peptone wat.	Serum
1	1-1′-Dimethylerythroapocyanine iodide	1 : 100 000 + 1 : 20 000 −	1 : 100 000 + 1 : 20 000 −	1 : 10 000 + 1 : 4000 −	1 : 20 000 + 1 : 10 000 −
2	1-1′-Dimethylxanthoapocyanine iodide	1 : 1000 000 + 1 : 400 000 −	1 : 400 000 + 1 : 100 000 −	1 : 10 000 + 1 : 4000 * −	1 : 100 000 + 1 : 20 000 −
3	1-1′-Diethylerythroapocyanine iodide	1 : 200 000 + 1 : 40 000 −	1 : 100 000 + 1 : 40 000 −	1 : 10 000 + 1 : 4000 −	1 : 20 000 + 1 : 4000 −
4	1-1′-Diethylxanthoapocyanine iodide	1 : 1000 000 + 1 : 400 000 −	1 : 40 000 + 1 : 200 000 −	1 : 40 000 + 1 : 5000 * −	1 : 100 000 + 1 : 2000 −
5	1-1′-8-8′-Tetramethylxanthoapocyaninenitrate	1 : 2000 000 + 1 : 400 000 −	1 : 1000 000 + 1 : 200 000 −	1 : 20 000 + 1 : 4000 * −	1 : 200 000 + 1 : 10 000 −
6	1-1′-6-6′-Tetramethylxanthoapocyaninenitrate	? + 1 : 200 000 −	? + 1 : 200 000 −	1 : 10 000 * + ? −	1 : 200 000 + 1 : 20 000 −
7	1-1′-Diethyl-6-6′-dimethylxanthoapocyaninenitrate	? + 1 : 400 000 −	? + 1 : 200 000 −	1 : 200 000 + 1 : 20 000 * −	1 : 200 000 + 1 : 40 000 −
8	1-1′-Dimethyl-6-6′-diaminoxanthoapocyanine iodide	1 : 200 000 + 1 : 100 000 −	1 : 400 000 + 1 : 40 000 −	1 : 40 000 + 1 : 20 000 * −	1 : 40 000 + 1 : 10 000 −
9	1-1′-Diethyl-6-6′-diaminoxanthoapocyanine iodide	1 : 400 000 + 1 : 100 000 −	1 : 400 000 + 1 : 40 000 −	1 : 2000 + 1 : 1000 −	1 : 100 000 + 1 : 10 000 −
10	1-1′-Dimethyl-5-5′-diaminoxanthoapocyanine iodide	1 : 100 000 + 1 : 20 000 −	1 : 100 000 + 1 : 20 000 −	1 : 10 000 * + 1 : 2000 * −	1 : 10 000 + 1 : 2000 −

TABLE 18.—*Relation Between Chemical Constitution and Antiseptic Action of Cyanine Derivatives.*—(Continued)

No.	Compound	*Staph. aureus*		*B. coli*	
		Peptone wat.	Serum	Peptone wat.	Serum
11	1-1′-Dimethyl-6-6′-dimethoxyxanthoapocyanine nitrate ..	1 : 1000 000 + 1 : 400 000 −	1 : 2000 000 + 1 : 100 000 −	1 : 20 000 * + 1 : 2000 * −	1 : 40 000 + 1 : 10 000 −
12	1-1′-Dimethylcarbocyanine iodide				
13	1-1′-Dimethylcarbocyanine chloride				
14	1-1′-Dimethylcarbocyanine nitrate				
15	1-1′-Dimethylcarbocyanine salicylate				
16	1-1′-Dimethylcarbocyanine acetate				
17	1-1′-Diethylcarbocyanine iodide				
18	1-1′-6-6′-Tetraethylcarbocyanine acetate	Results extremely variable on account of slight solubility; quite powerful antiseptics.			
19	1-1′-Dimethyl-6-6′-diaminocarbocyanine iodide				
20	1-1′-Dimethyl-6-6′-diaminocarbocyanine hydrochloride ...				
21	1-1′-Dimethyl-6-6′-dimethoxycarbocyanine iodide				
22	1-1′-Dimethyl-6-6′-dimethoxycarbocyanine acetate				
23	1-1′-Dimethyl-6-6′-diethoxycarbocyanine iodide				
24	2-2′-Diethylcarbocyanine iodide				
25	1-1′-Dimethylisocyanine iodide	1 : 2000 000 + 1 : 200 000 −	1 : 1000 000 + 1 : 100 000 −	1 : 400 000 + 1 : 200 000 −	1 : 200 000 + 1 : 40 000 −

26	1-1′-Diethylisocyanine iodide	1 : 1000 000 + 1 : 200 000 −	1 : 1000 000 + 1 : 100 000 −	1 : 20 000 + 1 : 4000 −	1 : 20 000 + 1 : 4000 −
27	1-1′-Dimethyl-6-aminoisocyanine iodide	1 : 400 000 + 1 : 200 000 −	1 : 400 000 + 1 : 200 000 −	1 : 200 000 + 1 : 10 000 −	1 : 100 000 + 1 : 20 000 −
28	1-1′-Dimethyl-6′-aminoisocyanine iodide	1 : 1000 000*+ 1 : 20 000* −	1 : 400 000 + 1 : 20 000 −	1 : 1000 * + 1 : ? −	1 : 40 000 + 1 : 4000 −
29	1-1′-Dimethyl-7-aminoisocyanine iodide	1 : 400 000 + 1 : 100 000 −	1 : 400 000 + 1 : 200 000 −	1 : 200 000 + 1 : 20 000 −	1 : 200 000 + 1 : 40 000 −
30	1-1′-Dimethyl-6-methoxyisocyanine iodide	1 : 2000 000 + 1 : 400 000 −	1 : 2000 000 + 1 : 400 000 −	1 : 40 000 + 1 : 20 000 −	1 : 100 000 + 1 : 40 000 −
31	1-1′-Dimethyl-6′-methoxyisocyanine iodide	1 : 1000 000 + 1 : 200 000 −	1 : 400 000 + 1 : 200 000 −	1 : 100 000 + 1 : 20 000 −	1 : 100 000 + 1 : 20 000 −
32	1-1′-Dimethyl-6-ethoxyisocyanine iodide	1 : 1000 000 + 1 : 200 000 −	1 : 400 000 + 1 : 200 000 −	1 : 100 000 + 1 : 20 000 −	1 : 40 000 + 1 : 20 000 −
33	1-1′-6-Trimethylisocyanine iodide	1 : 2000 000 + 1 : 400 000 −	1 : 2000 000 + 1 : 400 000 −	1 : 100 000 + 1 : 40 000 −	1 : 100 000 + 1 : 40 000 −
34	1-1′-6′-Trimethylisocyanine iodide	1 : 1000 000 + 1 : 200 000 −	1 : 1000 000 + 1 : 100 000 −	1 : 40 000 + 1 : 10 000 −	1 : 40 000 + 1 : 10 000 −
35	1-1′-6-6′-Tetramethylisocyanine iodide	1 : 4000 000 + 1 : 1000 000 −	1 : 1000 000 + 1 : 200 000 −	1 : 200 000 + 1 : 20 000 −	1 : 100 000 + 1 : 10 000 −
36	1-1′-6-6′-2′-Pentamethylisocyanine iodide	1 : 200 000 + 1 : 40 000 −	1 : 400 000 + 1 : 40 000 −	1 : 40 000 + 1 : 4000 −	1 : 40 000 + 1 : 20 000 −

+ Indicates free growth.
− Sterile cultures of the organisms in the concentrations indicated by the figures.
* Means precipitation of the antiseptic.

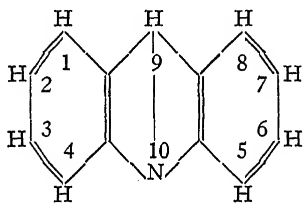
ferior to those obtained for staphylococci. In this group also, no distinct effect could be noted on the antiseptic action by alteration of the chemical structure.

The **isocyanine** derivatives studied also have powerful antiseptic properties for staphylococci, both in water and in serum. 1,1′-Dimethyl-6′-amino isocyanine iodide (28) is very slightly soluble in water, but its antiseptic action in serum is also rather weak although precipitation does not occur. By comparison with compounds (27; 31; 30; 33; 34; 35; 36) it appears that the side chain to the quinoline fraction of the molecule reduces the antiseptic action which is in contrast to the effect of their introduction in the quinaldine ring. Generally the effect of these compounds against staphylococci is more marked than against *Bacillus coli*, which difference is, however, less marked in serum than in peptone water.

Chapter XI.

Acridine Dyes.

Closely related to the quinoline dyestuffs are the acridine dyes, representatives of which have been studied for their chemotherapeutic action by Ehrlich and his school. These dyes have been extensively used especially by English physicians during the world war. They are derivatives of **acridine,** a substance isolated from coal tar.



Jodlbauer and Salvendi (**1905**) believed that acridine is excreted by the liver and by the kidney. Fuehner (**1904**) assumed that it is partly oxidized to oxyacridine and partly excreted as conjugated sulfuric or glucuronic acid.

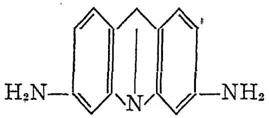
The toxic dose, according to Jodlbauer and Salvendi (**1905**), is 0.4 gram per kilogram for frogs. This causes central paralysis progressing from the cortex of the brain to the medulla and spinal cord. Consequently the respiration is slowed and shallow. The depression of the heart is presumably muscular; small doses may produce primary central stimulation.

Acridine causes marked irritation of the skin and of the mucous membranes without producing permanent pathological change. Jess (**1916**) reported severe changes of the retina similar to those observed after quinoline.

The antiseptic action on paramecia was studied by Raab (**1900**), who found that concentrations of 1:1000 killed immediately, concentrations of 1:10,000 in from 35 to 80 minutes; greater dilutions (1:20,000) required more than one hour. The intensity of

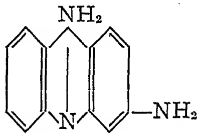
the reaction of the lowest concentration may be increased a hundred to a thousand times by strong light.

Introduction of amino groups in position 3- and 6- yields **3,6-diaminoacridine,**



According to Lenz (1921) this is about as toxic as trypaflavine for paramecia; concentrations of 1 : 760 kill the organisms immediately. Neufeld, Schiemann and Baumgarten (1920) found that its antiseptic action against gonococci is from one-third to one-tenth as strong as that of trypaflavine; it is also less effective against chicken cholera. Its effect against pneumococci and *Bacillus melitensis* is about the same as that of trypaflavine. According to Neufeld and Schiemann (1919) it disappears rapidly from the circulation. After the intravenous injection of the nitrate they could only detect one-thirtieth of the injected material after twenty minutes, and with the sulfate even less after ten minutes.

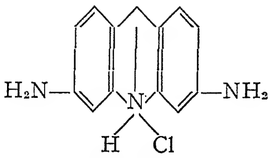
Morgenroth, Schnitzer and Rosenberg (1921) studied the antiseptic action of the isomer **6,9-diaminoacridine,**



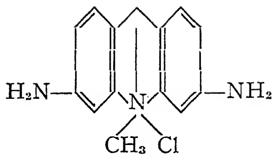
They found it very effective against different strains of streptococci in concentrations of 1 : 120,000 *in vitro; in vivo* concentrations of 1 : 10,000 were found to be still effective. The disinfecting quotient $\frac{\text{disinfecting value } \textit{in vitro}}{\text{disinfecting value } \textit{in vivo}}$ is therefore one-twelfth.

Acriflavine.

It has already been pointed out in the discussion of the quinoline dyes that the change of the trivalent to the pentavalent nitrogen increases the antiseptic efficiency. The same phenomenon may be observed by changing the trivalent nitrogen of the acridine ring into the pentavalent. The compounds thus obtained are:



proflavine



trypaflavine
flavine or *acriflavine*

The clinical usefulness of these compounds as local and general antiseptics has been much discussed, the *pros* and *cons* having been debated with equal vigor. Laqueur (1923) gives an extensive review of this literature, from which it appears that further studies and observations are necessary to settle the question of its usefulness.

The controversy begins with the question of the *toxicity* of these compounds. A dose of 200 mg. in the form of 0.1 and 0.5 per cent solutions and even more than twice this dose have been given intravenously without bad effects (Bohland, 1919). Treuherz (1930) observed anaphylactoid reactions after the administration of 250 mg. (5 cc. of a 0.5 per cent solution). According to Browning, Gulbranson and Thornton (1917) proflavine seems to be somewhat less irritant than trypaflavine with intraperitoneal injections. The minimal fatal dose for cats is also somewhat smaller. With intravenous administration, according to Tubby, Ferguson, Mackie and Hirst (1919), this is 11.1 mg. per kilogram for proflavine and 7.3 mg. per kilogram for trypaflavine. Heathcote and Urquhart (1930) gave the minimal fatal dose of acriflavine with intravenous injection as 30 mg. per kilogram for rabbits and dogs. The toxicity, however, depends largely upon the speed of the injection; if injected rapidly it produces respiratory failure by anaphylactoid reactions, caused by agglutination of the blood. Browning and Cohen (1921) gave the maximal tolerated dose per 20 grams mouse as 3 mg. of proflavine and 0.6 mg. of trypaflavine. Lenz (1921) determined the minimal fatal dose of trypaflavine as 80 to 100 mg. per 100 grams frog, while that of quinine was 40 to 50 mg.; it appears, therefore, that trypaflavine is about one-half as toxic as quinine. Lenz found that 40 mg. per 40 grams frog of trypaflavine produce severe depression of the central nervous system, very similar to that observed by Jodlbauer and Salvendi (1905) with acridine. Crittenden (1932) believed that the toxicity varies with different preparations and that a neutral acriflavine can be prepared which

has very little side action. She suggested that the toxicity of acriflavine preparations should be tested in animals before they are given intravenously in man.

Concentrations of acriflavine of 1:2000 produce immediate arrest of the isolated frog heart in diastole; dilutions of 1:4000 cause irregularities. Heathcote and Urquhart (**1930**) found that acriflavine in concentrations of from 1:10,000 to 1:1,000,000 depresses the isolated perfused heart of the toad by direct muscular action. Concentrations of from 1:20,000 to 1:50,000 have no effect on the smooth muscle of the blood vessels of the toad. Concentrations of from 1:50,000 to 1:250,000 were found to stimulate the isolated rabbit intestine by direct muscular action; more concentrated solutions of from 1:25,000 to 1:10,000 have a depressing effect. In the acute experiment trypaflavine has no very marked effect on the blood vessels, but with repeated administration it may damage the nerve endings in the arteries and also may affect the arterial muscle, thus producing an irreversible paralysis. Also the experiments of Crittenden seem to indicate that the fall of the blood pressure as observed after intravenous administration of acriflavine is mainly peripheral. Though trypaflavine is a quaternary base Lenz (**1921**) could not detect a curare action on the receptive mechanism of the muscle. Heathcote and Urquhart found that acriflavine in concentrations of 1:20,000 has no effect on the striated muscle of the toad, but higher concentrations of 1:3000 inhibit the response to direct electric stimulation.

Bohland (**1919**) found that one hour after the intravenous injection of trypaflavine into the circulation the number of the erythrocytes is reduced by half a million and that of the white blood cells is increased by one-half or may even be doubled; the number of lymphocytes shows the greatest increase. Lenz (**1921**) reported similar results for guinea pigs and rabbits. This is in contradiction with the results reported by Stephan (**1921**), who found that half an hour after intravenous administration the total leucocyte count is reduced, together with the absolute value of the myeloid cells. The number of the lymphocytes was not changed but the large mononuclear cells and the transitory forms showed a rapid increase and their number remained at a high level for some time. Meleney and Zau (**1925**) believed that the leucocytosis observed in rabbits after the intravenous injection of neutral acriflavine is proportional to the

amount of the dye injected, that it has little or no effect on the number and fragility of red blood cells nor has it any influence on the clotting and bleeding time. It has, however, a temporary deleterious effect on the functional activity of the polynuclear leucocytes. In test tube experiments Keysser (1919) observed a reduction of 25 per cent in the phagocytic processes in concentrations of 1: 10,000. Similar results were reported by Fleming (1917) and by Browning, Gulbranson and Thornton (1917). According to Browning and Cohen (1921) the antiseptic effect of trypaflavine is, however, already marked with concentrations 100 times more dilute than those which produce this antiphagocytic action. It has already been mentioned that trypaflavine causes agglutination of the red blood cells. According to Fleming (1917) this occurs with human blood cells in concentrations of 1: 32,000 but can be delayed by the addition of serum.

When injected into the circulation trypaflavine disappears rather rapidly from the blood. Neufeld and Schiemann (1919) found with intravenous injections in rabbits that after 15 minutes one hundred-thirtieth was present in the blood and after 30 minutes one two-hundreth. Similar results were reported by Tubby and his collaborators (1919); in 3 and in 30 minutes after the intravenous administration no dye could be detected in the serum nor could any antiseptic action of this blood be observed.

As to the *fate* of the injected material, animal experiments and clinical observations give different results. After large doses Tubby and his staff observed marked staining of the animals; Crohn (1920), Browning and Cohen (1921), and Haupt (1921) and others, also noticed staining of the skin, while Bohland (1919) did not observe any staining of skin or sclera. Gay and Morrison (1921) believed that trypaflavine is not stored in the muscle, while Stephan (1921) believed that the mesenchymatous tissues have a specific affinity for the dye. The question whether or not trypaflavine passes into the cerebrospinal fluid is also still under discussion. According to some investigators, as for instance Lenz (1921), it is present, although in small quantities; others like Bohland deny that it passes into the spinal fluid. Inflamed tissues seem, however, to be more permeable to trypaflavine, as indicated by the findings of Fleischmann (1922) that, in patients suffering from meningitis, the amount of trypaflavine in the cerebrospinal fluid is markedly increased.

The excretion of trypaflavine occurs mostly by the kidney, but

is very slow according to the observations of Browning and Cohen and the reports of Haupt (1921). On account of the slow excretion Davis (1921) found it very efficient in the treatment of cystitis. Some trypaflavine is also excreted by the bile and renders it bactericidal (Kauftheil and Neubauer, 1926; Browning and Cohen, 1921). After intravenous injection of trypaflavine, Haupt (1921) found some of the dye in vomited material. It is probably also excreted through other channels, as indicated by its presence in the mucus of the cervix. According to Haupt, Willisch (1920) demonstrated the presence of acriflavine also in amniotic fluid and in saliva.

It appears that antiseptic concentrations of trypaflavine are not *toxic* for tissues and that they even enhance regeneration of tissue (Ritter, 1920; Sheehan, 1930). Higher concentrations, however, may be injurious as demonstrated by Reinhardt (1922).

As regards the *antiseptic action* of trypaflavine special importance attaches to the observations of Browning and his school that this dye is more effective in serum than in serum-free aqueous solutions. The sensitivity of different organisms varies considerably; Ehrlich found it very effective in nagana infections of mice, but distinctly less in sleeping sickness and malaria. According to Neufeld and Schiemann (1919) gonococci and meningococci are highly sensitive to trypaflavine; coli, typhoid and influenza bacilli are very little sensitive. Nicoletti (1932) found in agglutination experiments with different strains of gonococci that these differ considerably as to the speed and intensity of agglutination. This may aid in the interpretation of the contradictory results reported in the literature on the treatment of such infections with trypaflavine. But even in those cases where it is effective, the action is rather slow, as was confirmed by Tubby and his staff, who found that it requires hours of contact to sterilize infected blood. Lenz (1921) reported that the toxicity of acriflavine for paramecia is distinctly higher than that of quinine. Tinker and Sutton (1927) advocated a 0.5 per cent solution of acriflavine in a mixture of acetone, alcohol and water (10:52.5:37.5) for disinfection of the skin. The antiseptic action *in vitro* may be considerably impaired by the presence of pus cells, for, according to Keysser (1921), 100 times more concentrated solutions are required to kill staphylococci and streptococci in cultures containing pus than in those containing serum. Gay and Morrison (1921) observed the opposite. Tagami (1932)

found that the bactericidal action of trypaflavine increases with the pH of the solution. The factors which may account for such contradictory results will be discussed later. Rivière and his collaborators (1931) reported that irradiation with ultraviolet light increases the antiseptic efficiency of acriflavine solutions *in vitro* against meningococci. With systemic administration such irradiated solutions also appear to be more effective.

Reports are rather contradictory on the efficiency of acriflavine with systemic administration. Neufeld and Schiemann (1921) reported favorable results with intravenous administration in gonococci and meningococci infections, and Keysser (1921) with pneumococci infections. Boyksen (1930) observed good results in typhoid in that the illness was shortened and the symptoms were less marked. Meyer (1930) studied the antiseptic action in puerperal infections with dogs and found that the intravenous injection of an appropriate dose has a definite beneficial effect which is more marked with early administration after the infection. Africa and Luckner (1931) observed good results with intravenous injections in rabbits infected with *Trichinella spiralis*. They assumed that the larvae circulating in the blood are killed by the drug. This could not be confirmed by Miller, McCoy and Bradford (1932) in rabbits suffering from trichinosis. On the other hand, Wels (1922) saw not a single clear-cut, favorable result after the intravenous administration of acriflavine in patients suffering from influenza and general septicemia. Meleney and Zau (1925) believed that the bacteriostatic action of neutral acriflavine against *Streptococcus hemolyticus* is so small that its intravenous administration to man in such infections cannot be considered legitimate.

Toxic symptoms after the intravenous injection of trypaflavine have been reported by different authors. Richet and Conder (1930) observed in two cases the development of uremic conditions and they, therefore, cautioned against the intravenous injection of trypaflavine in patients suffering from kidney disturbances and emphasized the importance of a frequent control of the urea level of the blood. Similar findings were reported by Kartagener and Ramel (1932). Levrat and Badinand (1931) observed also an increase of the blood urea in rabbits after the intravenous injection of acriflavine, corresponding in degree to the severity of the kidney lesions as found at autopsy. They believed that the toxicity varies with different brands of acriflavine

and are inclined to credit the toxic reactions to impurities. After intravenous injections of acriflavine Benard and Tanin (**1930**) saw in a patient the development of acute hepatic insufficiency together with cutaneous and visceral purpura. Birsh (**1931**) also reported several instances of liver damage after the intravenous injection of acriflavine. After the intravenous administration of acriflavine to dogs Heathcote and Urquhart (**1930**) observed changes in the kidney and in the liver, extensive destruction of erythrocytes and disturbances of the general metabolism. Meleney and Zau (**1925**) believed that acriflavine has a selective affinity for certain organs of the rabbit, from which it may be adsorbed to such an extent as to cause injury, which is especially marked in kidney and liver. Monasterio (**1931**) found that 0.08 gram per kilogram in rabbits and 0.04 gram per kilogram in dogs cause hypoglycemia which can be overcome by the intravenous injection of sugar, and it also antagonizes the hyperglycemia produced by removal of the pancreas. This hypoglycemia is therefore not due to a hypersecretion of insulin. Experiments with rats indicate that the liver glycogen is involved in this reaction, that it inhibits perhaps the oxidative synthesis of carbohydrates and that its action, therefore, resembles that of other quinoline derivatives.

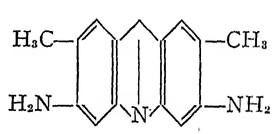
The **iodomethylate** of proflavine, **iodoflavine,** is, according to Hata (**1932**), about one-half as toxic and effective as trypaflavine. He believed that the penetrating and staining properties of these dyes are closely connected with the 3,6- diamino groups.

Mietsch and Maus prepared a **substituted alkylaminoalkylamino acridine** derivative which was synthesized on the basis of the experiences made with plasmoquine. It is marketed under the name of **Atebrine.** The chemical constitution of this compound has not yet been published; it is a yellow powder, melting at 245° to 255° C. with decomposition. It is soluble in water up to 7 per cent at 40° C., the aqueous solution having a neutral reaction. According to Kikuth (**1932**) experiments with birds infected with *Plasmodium praecox* showed that it is less toxic and also 15 times less effective than plasmoquine but 4 times more active than quinine. In contrast to plasmoquine it does not affect the gametes but kills the schizont forms and therefore its combination with plasmoquine appears advisable. Strickland and Roy (**1932**) fed mosquitoes on malaria-infected patients at different intervals after the administration of atebrine. They

found that the drug completely prevents the development in the mosquito of any gametocytes from the human host, that considerable inhibition to development persists the day after the drug has been discontinued and that the parasite resumes its developmental power only three days after discontinuation of atrebine. Sioli (1932) tested it in inoculation malaria of paralytic patients. He found that 0.1 gram 3 times daily for 3 days caused complete cure in 86 patients. It appears that the action is more lasting than with quinine or plasmoquine, the administration of which for not more than 3 days is liable to permit relapses. He considers atebrine in this respect 4 times more effective than plasmoquine. Single doses of 0.2 gram or a total dose of 0.6 gram is tolerated without side actions. Larger doses may cause occasional gastro-intestinal disturbances. During the atebrine treatment the patient may develop a yellow coloration of the skin which is not of icteric character but which is caused by the dyestuff. This is only temporary and according to most observers disappears within from 8 to 15 days. The curative value of this compound was also confirmed by Peter (1932), who used it successfully in tertian malaria and in malaria tropica. Muehlens (1932) tested atebrine in 120 patients and observed no side actions, using a total dose of from 4 to 8 grams. He reported good results in 17 cases of tertian malaria, in 8 cases of quartan malaria and in 85 patients suffering from malaria tropica. The moderate effect on gametocytes is especially marked in malaria tropica where the combination of atebrine with plasmoquine seems to be an ideal remedy. Although treatment for 3 to 5 days showed no relapses he suggests continuing the administration of the drug especially in the tropics for at least from 7 to 10 days, giving 0.1 gram of atebrine 3 times daily together with 0.01 gram of plasmoquine. He believed that in very severe cases of malaria tropica with numerous ring forms the simultaneous administration of quinine during the first 2 days is indicated. He further mentions that in cases of quinine idiosyncrasy and in blackwater fever atebrine is very well tolerated. Green (1932) treated 50 malaria patients with atebrine and 46 with quinine. He found that atebrine compares favorably with quinine in ridding the blood of malaria parasites and in relieving the symptoms, and that it is superior in preventing a relapse. From a small number of patients he heard complaints about abdominal pain. He ob-

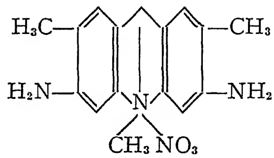
served the yellow discoloration of the skin only with large doses and sparing urinary excretion. In his opinion the administration of atebrine over a period of 7 days destroys the gametocytes of *Plasmodium vivax* with sufficient rapidity to prevent mosquitoes from being infected by benign tertiana cases within from 3 to 4 days after the beginning of the treatment. He started the treatment with a purgation and gave daily 0.1 gram per 15 kilograms body weight for from 6 to 7 days, controlling the urinary excretion of the dye in order to prevent its accumulation. Napier and Das Gupta (**1932**) found that, in all 3 types of plasmodial infections, atebrine in doses of 0.1 gram 3 times daily for 4 days controls the fever, brings about the disappearance of the asexual forms of the parasite from the peripheral blood and that in such doses it has neither an unpleasant taste nor toxic side actions. From their limited number of cases they believe that atebrine does not act as rapidly as quinine. In one case studied in regard to the prophylactic value of atebrine it appears that a single dose of 0.1 gram is of distinct benefit. Napier, Butcher and Das Gupta (**1932**) treated 35 patients suffering from malign and 13 infected with benign malaria with 1.2 grams of atebrine in a 4 day course followed by 0.06 gram of plasmoquine in a 3 day course and observed only 5 and 2 clinical relapses, some of which may have been reinfections. In only 1 out of 41 cases were malaria parasites found in the peripheral blood immediately after the end of the treatment. Good results were also reported by Orenstein (**1932**).

Introduction of two methyl groups in position 2- and 7- yield **2,7-dimethyl-3,6-diaminoacridine, acridine yellow,**



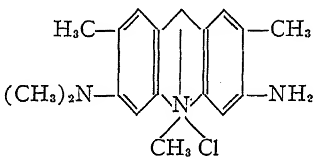
According to Ehrlich and Werbitzki (**1910**) this has only slight trypanocidal action, less so than the following compound. Lenz (**1921**) found about the same toxicity for paramecia as with trypaflavine, nor is it markedly different in regard to its irritant action on the rabbit cornea. According to Browning and Gilmour (**1913**) it is less effective than the unsubstituted diaminoacridine.

The corresponding methonitrate, **brilliant phosphine nitrate,**



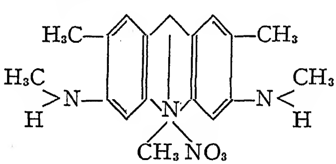
shows no essential difference as to its toxicity for paramecia or in regard to its irritant action as compared with the two preceding compounds.

Methylation of the 3- amino group and of the 2,7- carbons of trypaflavine yield **2,7-dimethyl-3-dimethylamino-6-aminoacridine methochloride.**



This was advocated by Langer (1920) as an antiseptic. The tolerated dose for rabbits is 0.25 gram per kilogram and the minimal fatal dose 0.3 gram per kilogram. It kills staphylococci in concentrations of from 1 : 100,000 to 1 : 1,000,000 within one hour, while trypaflavine under the same conditions requires much higher concentrations, namely 1 : 32,000 to 1 : 200,000. Like trypaflavine, but less markedly, this compound is excreted with the bile which is rendered antiseptic for *Staphylococcus aureus* but not for *Bacillus coli* (Kauftheil and Neubauer, 1926).

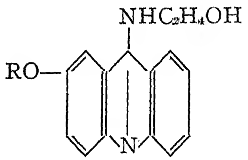
The **2,7-dimethyl-3,6-methylaminoacridine methonitrate, brilliant phosphine imino,**



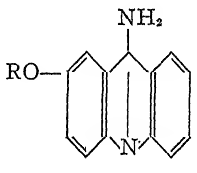
is an isomer of the former, and according to Langer (1920) resembles trypaflavine in its toxicity for paramecia. The minimal fatal dose for mice is 340 mg. per kilogram by intraperitoneal injection according to Lenz (1921). This compound seems to be somewhat less toxic than trypaflavine, the minimal fatal dose of which is 250 mg. per kilogram. However, with intravenous ad-

ministration in rabbits it was found to be about 8 times as toxic as trypaflavine. The toxic phenomena resemble those observed after trypaflavine very closely, but the motor paralysis is said to occur earlier and the depressant effect is more marked than with trypaflavine. The toxicity is about the same for both dyes.

Morgenroth, Schnitzer and Rosenberg (**1921**) studied a series of acridine derivatives which, in addition to the aminoethanol group in position 9-, contained an alkyloxy group in position 2-,



In this formula *R* was replaced by methyl, ethyl, allyl, propyl, isobutyl and isoamyl groups. From test tube experiments it appeared that the allyloxy and the ethoxy compounds had marked antiseptic properties for streptococci, the minimal fatal concentration of the former being 1 : 100,000, that of the latter 1 : 80,000. In animal experiments, however, the ethoxy compound was found to be six times more effective than the allyl derivative but it failed to show any effect against a culture of fresh streptococci from man. Browning and Cohen (**1921**) had already pointed out that introduction of alcoholic groups into the amino group reduces the antiseptic action and Morgenroth tried, therefore, the corresponding unsubstituted amino derivative, **2-ethoxy-9-aminoacridine,**

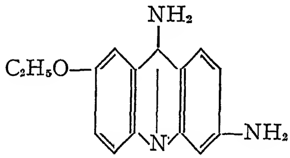


This compound has bactericidal properties in a concentration of 1 : 160,000, but it has proved effective only against certain strains and has failed to show pantherapeutic properties.

Rivanol.

This failure was overcome by the introduction of a second amino group in position 6-. This compound, **2-ethoxy-6, 9-diaminoacridine,** was found to be very effective and its hydro-

chloride is used clinically under the name of **Rivanol.** It has been mentioned that the 6,9-diaminoacridine,



has the disinfecting quotient, $\frac{\text{disinfecting value } in\ vitro}{\text{disinfecting value } in\ vivo}$ = one-twelfth. The 2-ethoxy-6,9-diaminoacridine is effective against streptococci *in vitro* in concentrations down to 1: 120,000 and the effective dose *in vivo* was found to be 1:40,000 or less, so that the disinfecting quotient is higher than one-half and for certain strains even as high as one. Schnitzer and Rosenberg (**1922**) tested rivanol with 231 different strains without finding one which was rivanol-resistant. Laqueur, Sluyters and Wolff (**1924**) tested its efficiency with different streptococci, some of which were old laboratory strains and some fresh cultures isolated from human infections. They found the minimal effective concentration to vary between 1: 20,000 and 1: 100,000; one of their strains was found to be refractory, and therefore rivanol cannot be considered a pantherapeutic antiseptic in the strict sense of the word. Concentrations of from 1: 16,000 to 1: 64,000 were also quite effective against *Bacillus coli.* Browning and Gulbranson (**1928**) compared its antiseptic action for streptococci with that of trypaflavine and found it somewhat less effective.

The experiments concerning the curative value of rivanol in infected animals showed its distinct value, as already pointed out by Morgenroth and his co-workers, and this was confirmed by Laqueur and his staff, especially when the drug was given shortly after the infection. In comparing the efficiency of rivanol and trypaflavine *in vivo* Browning and Gulbranson (**1928**) could not obtain definite results on account of the individual variations of their animals.

Lim and Kurotchkin (**1930**) studied the fungicidal properties. They found it only slightly effective *in vitro* against *Monilia tropicalis* and stated that *in vivo* it could not prevent the development of fatal mycotic septicemia in rabbits. Biggam and Arafa (**1930**) saw no curative effect in dysentery with local treatment using concentrations of 1: 10,000; after oral administration of

0.075 gram 3 times daily there were no toxic symptoms but also no indication of a curative effect. Miller, McCoy and Bradford (1932) found rivanol ineffective in preventing heavy muscular infection of rabbits suffering from trichinosis although they used larger doses than of acriflavine.

Morgenroth claimed that the antiseptic properties of rivanol were not impaired by the presence of serum, but Laqueur found that pure serum is inhibitory and that in the presence of pus, blood and also of muscle pulp the antiseptic action of the compound is very markedly reduced.

Laqueur, Sluyters and Wolff (1924) studied the effect of changes of the pH on the antiseptic action of rivanol and found that this increases with the pH from 1:20,000 at pH 5.95 to 1:500,000 at pH 8.0. Similar results were reported by Tagami (1932). Since the hydrogen ion concentration of pus is markedly higher than that of normal serum or tissue fluids the reduction of the pH may account for the loss of activity, but the effect was the same in acid or in neutralized pus, so that some other factor must be credited with the inhibitory action.

According to Janzen and Wolff rivanol depresses bacteriophagic processes; the concentration varies from 1:5000 to 1:10,000, depending on the type of the bacteriophage.

Laqueur, Sluyters and Wolff (1924) tried to develop rivanol resistance in streptococci exposed to rivanol but without success, at least within 23 days. On the other hand, they found that streptococci exposed to rivanol for some time showed no resistance against trypaflavine after 14, but a very distinct one after 19 days, while their sensitivity for rivanol had not been changed.

Opinions as to the *irritant action* of rivanol diverge widely. Rosenstein (1921) never noticed irritation, Klapp (1921) stated that infiltrations with 1:1000 are so painful that such injections have to be performed under local or general anesthesia. He also found that rivanol causes inflammatory reactions. This was confirmed by Laqueur, who saw marked infiltration in rabbits with intracorneal injections of solutions of 1:1000, which was not produced by the same concentration of trypaflavine. Katzenstein and Schulz (1922) observed good results and little irritation in diffuse peritonitis. Biggam and Arafa (1930) noted local irritation and marked hyperemia of the lower intestine after irrigation with concentrations of 1:2000.

As to the *distribution* of rivanol in the blood, Laqueur, Sluyters

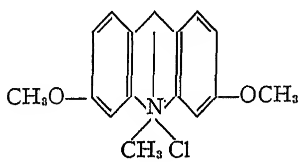
and Wolff (1924) found in test tube experiments that after 24 hours, about one-half of the drug had disappeared from the serum and that the red blood cells contained about 3.5 times more than the serum. They also found that concentrations from 1 : 6400 to 1 : 200 with a median value of 1 : 1000 produced agglutination of human blood varying in degree with different individuals. Under the same conditions the minimal effective concentration of acriflavine was 1 : 400. Hemolytic action could only be observed in higher concentrations.

Data as to the *excretion* of rivanol are rather scanty. Kauftheil and Neubauer (1926) found that it is partly excreted with the bile which is rendered antiseptic for staphylococci but not for *Bacillus coli*, being on the whole less effective than trypaflavine in this respect.

Morgenroth, Schnitzer and Rosenberg (1921) determined the tolerated dose for mice as 0.3 cc. of a 1 : 200 solution, given subcutaneously; 0.5 cc. of 1 : 600 given intraperitoneally; and 0.5 cc. of 1 : 500 intravenously. Browning and Gulbranson (1928) found with subcutaneous administration that 1 cc. of a 1 : 1000 solution may already produce toxic symptoms. Laqueur reported that the intravenous injection of 50 mg. per kilogram rabbit is immediately fatal by respiratory arrest; with slow injection, however, larger doses may be given, but 80 mg. per kilogram always proved to be fatal.

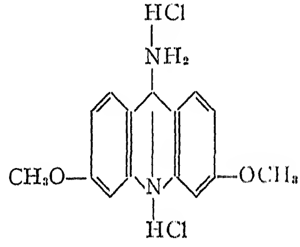
As to the systemic action of rivanol, Laqueur (1923) observed with intravenous injection a short fall of blood pressure with rapid return to normal. According to Gessner (1929) the isolated frog heart is arrested by concentrations of 1 : 1000 in 1.6 minutes when exposed to light, and in 16 minutes when kept in the dark. The cardiac effect was found to be irreversible. He also found that concentrations of 1 : 20,000 paralyze the salamander immediately, higher dilutions (1 : 40,000) paralyze after 6 hours, the paralysis being reversible. The depressant effect on the intestinal activity is not uniform and not as marked as was assumed by Schaumann (1928).

3,6-Dimethoxyacridine-10-methochloride, sinflavine,



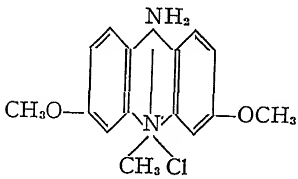
has no staining properties on account of the absence of amino groups. According to Hata (1932) it is about one-half as toxic as trypaflavine having at the same time an equal curative value. The minimal bactericidal concentration for *Streptococcus hemolyticus* and *Staphylococcus aureus* in bouillon and in serum bouillon is 1:729,000. The maximal tolerated dose for mice, given intravenously, is 1 cc. of a 1:1500 solution, the minimal sterilizing dose is 1 cc. of a solution of 1:5000 to 1:10,000 and the therapeutic index $\frac{\text{maximal tolerated dose}}{\text{minimal sterilizing dose}}$ is between 1/3.3 and 1/6.7. Tissues may grow in concentrations up to 1:12,000 and solutions of 1:18,000 prevent the infection of tissue cultures with bacteria.

Introduction of an amino group in position 9- of sinflavine yields **9-amino-3,6-dimethoxyacridine dihydrochloride,**



This compound consists of slightly yellow needles soluble in 200 parts of water at room temperature. The aqueous solution is light yellow and shows light violet fluorescence in higher dilutions which have no staining properties. Like sinflavine it is precipitated from its aqueous solution by means of sodium chloride and therefore physiologic saline has to be avoided. According to Hata (1932) it is one-third as toxic as trypaflavine, the antiseptic action being equal. It kills *Streptococcus hemolyticus* and *Staphylococcus aureus* in concentrations of 1:729,000 both in bouillon and in serum bouillon. The maximal tolerated dose intravenously for mice is 1 cc. of a 1:1200 solution; the minimal sterilizing dose is 1 cc. of a 1:5000 to 1:10,000 solution, the therapeutic index being, therefore, 1/4.1 to 1/8.3. The maximal concentration in which tissue cultures will grow is 1:8000 and a concentration of 1:40,500 prevents the infection of these cultures.

The corresponding methochloride, **9-amino-3,6-dimethoxy-acridinium methochloride,**



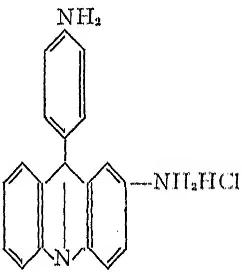
consists of fine yellow needles soluble in 300 parts of warm water. The aqueous solution is more intensely yellow than that of the hydrochloride and shows also a more intense bluish-green fluorescence. It has no staining properties and it is also precipitated by sodium chloride. The bactericidal action and the maximal tolerated dose is the same as that of the hydrochloride; the minimal sterilizing dose is, however, 1 cc. of a 1: 10,000 to 1: 20,000 solution, and the therapeutic index is, therefore, 1/8.3 to 1/16.3. This compound is therefore of the same therapeutic value as trypaflavine without having the staining properties of the latter.

Chapter XII.

Phosphines.

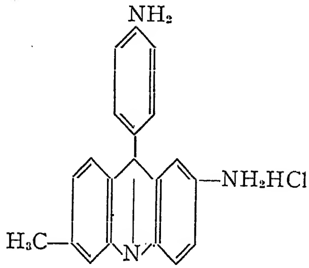
Phosphines are acridine derivatives in which the hydrogen in position 9 is replaced by a phenyl group. They are side products in the preparation of fuchsin and most of them are soluble in water and in alcohol with reddish-yellow to green colors; their solutions show marked fluorescence.

Diaminophosphine, chrysaniline,



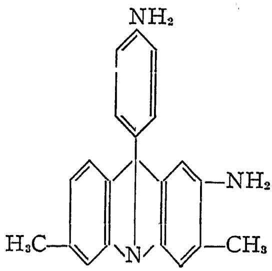
Ehrlich (1907) found this to be ineffective against trypanosomes. According to Tappeiner (1895) it kills paramecia in concentrations of 1:25,000 in 20 to 25 minutes; amebae and turbelariae are equally sensitive and yeast more resistant. Its toxicity is, however, markedly increased in strong light. Dadlez and Kokowski (1930) reported that in dogs the intravenous injection of 25 cc. of a saturated solution of the dye increased the body temperature from 36° to 40.3° C. From metabolic studies they concluded that this fever is due to increased carbohydrate metabolism. With the same dose non-chloralized dogs show convulsions and respiratory difficulties. During the convulsive stage there is no rise of the temperature, which may be actually reduced. But as soon as the respiration is adequate, fever may be observed.

According to Tappeiner (1895) the **monomethylphosphine,**



kills paramecia in concentrations of 1:25,000 within 7 or 8 minutes. This compound was tested by Mannaberg (1897) as to its antimalarial action, but it had to be discarded on account of the yellow staining of the skin observed after its administration. *In vitro* it was found to be less effective than quinine against plasmodia.

The **dimethyl-diaminophosphine, benzoflavine,**



was also tested by Tappeiner and has the same toxicity for paramecia as the preceding compound. Concentrations of 1:25,000 kill the organisms in from 7 to 9 minutes. The systemic action of both compounds was studied by Jodlbauer and Fuerbringer (1897), who found that they produce a short respiratory stimulation, followed by depression and by paralysis of the respiratory center. They also observed clonic convulsions primarily due to stimulation of the spinal cord, although the higher centers may also be involved. Neither drug has marked effect on the circulation. Locally higher concentrations produce irritation. The dimethyl compound appears to be more toxic than the monomethyl derivative.

Relation between Chemical Constitution and Pharmacologic Action of Acridine and Phosphine Dyes.

Comparison of changes of the chemical constitution of acridine derivatives with their antiseptic properties shows the following relation:

Introduction of amino groups in the two benzene rings or in carbon 9 increases the antiseptic action as in acridine and diaminoacridine and in 2-ethoxy-6,9-diaminoacridine as was already pointed out by Browning and Cohen for the first two compounds.

Transformation of the acridine compounds into acridinium derivatives increases the antiseptic action, the methochloride being generally more effective (3,6-diaminoacridine; 3,6-diaminoacridinium hydrochloride (proflavine); 3,6-diaminoacridinium methochloride (trypaflavine).

Introduction of a methyl group into the acridine ring does not increase the antiseptic action markedly (trypaflavine, acridine yellow, brilliant phosphine nitrate). Browning and Gilmour believed that this causes a reduction of the antiseptic properties, diaminoacridine being more effective than acridine yellow. In the phosphine group Tappeiner and his school noted an improvement of the antiseptic action by the introduction of methyl groups because they found monomethyl and dimethylphosphine more effective than phosphine.

Substitution of the hydrogen of the amino group by methyl radicles in one amino group increases the antiseptic action in some instances (flavicid, trypaflavine); with the substitution of one hydrogen in each of the two amino groups the effect is, however, less marked (flavicid, brilliant phosphine imino). Browning believed that substitution of the amino hydrogen by methyl radicles generally decreases the antiseptic action and that introduction of acetyl and alcohol groups abolishes it completely or at least markedly reduces it (2-ethoxy-9-aminoacridine, 2-ethoxy-9-aminoethanolacridine).

According to Browning and Cohen introduction of a phenyl group in position 9- decreases the efficiency (2,7-diamino-3,6-dimethylacridine being more effective than 2-amino-3-methyl-9-naphthylacridine). Jodlbauer and Salvendi found 9-phenylacridine less effective against paramecia than the corresponding methyl compound. That this is not a strict rule may be seen by the

fact that the methochloride of 9-phenyl acridine is more effective than acridine as pointed out by Browning.

From this comparison it appears that the relation between chemical constitution and pharmacologic action is less distinct in this series than with the hydrocupreine derivatives. Different organisms show a different sensitivity towards the same compound. The action is generally slow as pointed out by Neufeld and his collaborators, by Burkhardt and Dorn and others, and, therefore, variations in the determination of the minimal effective concentration are not infrequent. Besides, it has been found that the number of organisms exposed to the antiseptic also affects the efficiency. It appears, therefore, that physico-chemical phenomena rather than chemical reactions with the bacterial organisms are involved in the antiseptic action of these compounds. Abelmann and Liesegang (1918) had already pointed out that dyes with the most heterogeneous receptors and the most different constitutions showed the same biological behavior in vital staining. They found that in addition to their lipoid-solubility the degree of diffusibility was important in this matter since dyes with moderate diffusibility or without diffusibility produce only local staining of the site of their injection. Those which diffuse more readily produce general staining. With these the ratio between staining, storage and discoloration is especially favorable, whereas with highly diffusible dyes both staining and discoloration occur very rapidly. Similar conclusions were reached by Bilz and Pfennig (quoted from Schulemann), who found that molecules of similar structure containing up to 45 atoms dialyzed rapidly, those containing from 45 to 50 rather slowly, those containing from 55 to 70 showed little or no dialysis and compounds containing more than 70 atoms did not dialyze at all. They also found that sulfonation of such compounds not only increased the solubility but also enhanced their dialysis, so that substances with high molecular weight diffuse more readily. The effect of the introduction of one sulfonic group is usually more marked than that of subsequent introduction of the same group. That such substitution also affects the antiseptic action may be seen from Browning's studies on the effect of sulfonation on the bactericidal action of quinoline dyes which is distinctly improved by this chemical change.

Langer (1921) found that the antiseptic action of acridine dyes increases with the molecular weight rather than with changes in

the constitution and that a decrease of the dispersion increases the antiseptic action, while a finer subdivision has the opposite effect. He also pointed out that the dispersion depends on the pH, being reduced by increased pH and enhanced by decreased pH. The favorable effect of serum on the antiseptic action of some of these dyes may, therefore, be due to a decrease of the dispersion. Decreased dispersion results in an increased precipitation on the surface of the organisms or of the cells and hence develops more marked antiseptic action. The increase of the antiseptic efficiency by decreasing the dispersion is, however, limited by the fact that the diffusibility of a dye changes in inverse direction to the dispersion as already pointed out by Abelmann and Liesegang. On the other hand, Wels (1922) emphasized that rapid diffusion of dyes results in their storage in the tissue, thus rapidly reducing their effective concentration in the blood. This varies with different dyes and different cells. Hahn and Remy (1922) found, for instance, that 100 grams of moist *Bacillus coli* substance absorbs 2.69 grams of trypaflavine as compared with 1.37 grams absorbed by an equal weight of moist liver pulp. The optimal effect of acridine dyes depends, therefore, on the relation between the degree of their dispersion to that of the physico-chemical properties of the organisms.

The work of Laqueur, Sluyters and Wolff has shown that the pH of the medium may be of great influence on the antiseptic action of acridine dyes. They found that the bactericidal action of rivanol is 25 times greater at pH 8.0 than at pH 5.95. Similar results were reported by Browning, Gulbranson and Kennaway and by Davis and White for the antiseptic action of acriflavine in urine. This seems, however, not to be a general phenomenon because Michaelis and Hayashi (1923) found that trypaflavine was influenced only slightly or not at all in its antiseptic action by variations of the pH between 5.2 and 8.4, while with rivanol under the same conditions the minimal antiseptic concentration was 32 times as high as pH 8.4 as at pH 5.2. While trypaflavine shows practically no change of the surface tension within this range of the pH, rivanol shows after moderate alkalinization a slight decrease returning to the normal level with the addition of more alkali.

It appears, therefore, that the antiseptic action of acridine dyes depends partly on their diffusibility, partly on the degree of their dispersion which affects the surface tension and the adsorption

by microorganisms and the cells of the tissues. Since it was repeatedly found that the presence of cellular structures, such as blood or pus, reduces the antiseptic action of acridine dyes, and since Wels has shown that a similar reduction occurs in the presence of pieces of different organs immersed in the antiseptic solution, this may explain why the antiseptic action of dyes is largely reduced when injected into the circulation, and that under certain conditions the antiseptic action may even be reversed, namely, when in this way very low concentrations are produced which may have no antiseptic properties but which may interfere with the autobactericidal action of the serum.

It has been shown in the foregoing that the relation between chemical structure and pharmacologic action can only be established for compounds which are chemically related, although certain changes of the chemical structure affect the pharmacologic action of many different drugs in the same direction. In judging the efficiency of compounds, not only the pharmacologic action proper, but also their fate in the organism, i.e., their resistance towards metabolic processes must be considered. The physicochemical properties and the changes produced in these by variations of the molecular structure evidently require more study; this holds true especially for compounds of high molecular weight, where these qualities appear to be more predominant than with compounds of simpler structure.

Finally it appears that not infrequently physiologic problems are attacked by methods which appear to be extremely unphysiologic, so that only distorted pictures may be observed which may lead to misleading conclusions.

Bibliography.

Abelmann and Liesegang, Trypaflavine, *Dermatol. Wochenschr.*, **67**: 697 (1918).

Abl, R., Uric acid excretion, *Arch. exptl. Path. Pharmakol.*, **74**: 119 (1913).

Abraham, J. H., Acriviolet, *Laryngoscope*, **35**: 637 (1924).

Acton, H. W., Quinine, *Indian J. Med. Research*, **8**: 741 (1920/21).

Acton, H. W., R. N. Chopra, Quinine, *Indian J. Med. Research*, **13**: 197 (1925).

Acton, H. W., W. King, Quinine, *Biochem. J.*, **15**: 53 (1921).

Aeschlimann, J. A., M. Reinert, oxyquinoline, *J. Pharmacol.*, **43**: 413 (1931).

Africa, C., I. T. Luckner, Neutroflavine, *Proc. Soc. Exptl. Biol. Med.*, **28**: 432 (1931).

Akamatsu, M., Quinine, *Okayama-Igakkai-Zasshi*, **43**: (3), 494 (1931).

Akamatsu, T., Quinine, *Jikken Yakubuts. Zasshi*, **3**: 361 (1931).

Akashi, M., Quinine, *Arch. Schiffs Tropen-Hyg.*, **27**: 12 (1923).

Albertoni, P., Quinine, *Arch. exptl. Path. Pharmakol.*, **15**: 272 (1882).

Andant, A., Quinine, *Bull. Sci. Pharmacol.*, **37**: 89 (1930).

Anderson, H. H., N. A. David, D. A. Koch, Quinolinol, *Proc. Soc. Exptl. Biol. Med.*, **28**: 484 (1931).

Anderson, S. D., D. P. Teter, Cinchophen, *J. Am. Med. Assoc.*, **93**: 93 (1929).

Aoki, K., Quinine, *Folia endocrin. jap.*, **3**: 1331 (1928).

Appert, J., Quinine, *Virchow's Arch.*, **71**: 364 (1877).

Arbrink, N., Yatren, *Compt. rend. soc. biol.*, **97**: 1631 (1927).

Arendt, W., Yatren, Inaug. Diss. Hannover, **1922**.

Arndt, Th., Cinchophen, Inaug. Diss. Breslau, **1914**.

Arrillaga, F., J. Gugliemetti, C. P. Waldorp, Quinidine, *Compt. rend. soc. biol.*, **75**: 683 (1921).

Ash, R., Myer Solis-Cohn, Quinine, *J. Infectious Diseases*, **45**: 449 (1929).

Averbruck, S. H., Quinine, *Arch. exptl. Path. Pharmakol.*, **157**: 330 (1930).

Bachem, C., Quinine, *Therap. Monatsh.*, **24**: 532 (1910).

Bachstez, M., L. de Caro, Quinotoxine, *Arch. exptl. Path. Pharmakol.*, **164**: 314 (1932).

Baecker, J., Quinine, *Deutsch. med. Wochenschr.*, **31**: 417 (1905).

Baermann, G., Hydroquinine, *Arch. Schiffs Tropen-Hyg.*, **18**: 293 (1914); Beiheft (2) 37 (1914).

Baeyer, C., Quinoline, *J. prakt. Chem.*, second series, **33**: 393 (1886).

Baeyer, C., Quinoline, *Ber.*, **12**: 460 (1879).

Bailey, C. F., S. M. McElvain, Quinoline, *J. Am. Chem. Soc.*, **52**: 4013 (1930).

Baker, J. N., D. G. Gill, Plasmoquine, *U. S. Pub. Health Rept.*, **47**: 2245 (1932).

Bamberger, E., F. Lengfeld, *Ber.*, **23**: 1138 (1890).

Barber, M. A., W. H. W. Komp, Plasmoquine, *United Fruit Co. Ann. Rept.*, **16**: 54 (1927).

Barber, M. A., W. H. W. Komp, B. M. Newman, Plasmoquine, *United Fruit Co. Ann. Rept.*, **17**: 34 (1928).

Barber, M. A., W. H. W. Komp, B. M. Newman, *U. S. Pub. Health Rept.*, **44**: 1409 (1929).

Barbour, H. G., E. Lozinsky, Neocinchophen, *J. Lab. Clin. Med.*, **8**: 217 (1923).

Barbour, H. G., E. Lozinsky, C. Clements, Neocinchophen, *J. Med. Sci.*, **165**: 708 (1923).
Barbour, H. G., E. S. Wing, Quinine. *J. Pharm.*, **5**: 105 (1913).
Bass, R., Cinchophen, *Arch. exptl. Path. Pharmakol.*, **76**: 40 (1914).
Bass, C. C., Quinine, *Am. J. Trop. Med.*, **2**: 289 (1922).
Bass, C. C., Quinine, *J. Am. Med. Assoc.*, **95**: 988 (1930).
Bauereisen, Yatren, *Centr. Gynecol.*, (34) 1921.
Baur, J., Revellet, Bocca, Tulasne, Quinine, *Bull. mém. soc. méd. hôp. Paris*, **42**: 706 (1918).
Beaver, D. C., H. E. Robertson, Cinchophen, *Am. J. Path.*, **7**: 237 (1931).
Behring, von, Quinoline blue, *Z. Hyg.*, **7**: 173 (1889).
Behrle, E., O. Riddle, Quinine, *Am. J. Phys.*, **50**: 364 (1919).
Benard, R., M. Tanin, Acriflavine, *Bull. mém. soc. méd. hôp. Paris*, **54**: 1804 (1930).
Bendix, A., Cinchophen, *Therap. Gegenw.*, **14**: 301 (1912).
Berezin, Quinine, Ref., *J. Am. Med. Assoc.*, **67**: 844 (1916).
Bergami, G., Cinchophen, *Bull. soc. ital. biol. sper.*, **5**: 53 (1930).
Berger, E., Optoquine, *Arch. Schiffs. Tropen-Hyg.*, **43**: 423 (1926).
Berger, E., Quinine, *Centr. Immunitäts.*, **47**: 423 (1926).
Berger, S. S., H. H. Schweid, Cinchophen, *Med. J. Record*, **136**: 50 (1932).
Biach, A., G. Loimann, Quinoline, *Arch. path. Anat.*, **86**: 456 (1881).
Biberfeld, J., Quinine, *Arch. exptl. Path. Pharmakol.*, **79**: 361 (1916).
Biddau, E., Plasmoquine, *Rivista malariol.*, **9**: 53 (1930).
Biddle, H. C., Quinine, *J. Am. Chem. Soc.*, **34**: 500 (1912).
Bieling, R., Vuzine, *Berlin. klin. Wochenschr.*, **1917**, 1213.
Bieling, R., Cupreines, *Biochem. Z.*, **85**: 188 (1918).
Biggam, A. G., Quinine, *Brit. Med. J.*, **1**: 1171 (1930).
Biggam, A. G., M. A. Arafa, Acridine, *Lancet*, **218**: 1335 (1930).
Bijlsma, N. G., Vuzine, *Z. ges. exptl. Med.*, **11**: 257 (1920).
Binz, A., C. Räth, Oxyquinoline, *Biochem. Z.*, **203**: 218 (1928).
Binz, V. C., Quinine, *Arch. path. Anat.*, **46**: 67, 129 (1869).
Binz, V. C., Experimental studies on the principle of the action of quinine, Berlin, **1868**.
Binz, V. C., Quinine, *Arch. exptl. Path. Pharmakol.*, **1**: 18 (1873); **5**: 39 (1876); **7**: 275 (1877).
Birsh, C. A., Acriflavine, *Lancet*, **220**: 269 (1931).
Bischoff, H., Yatren, *Deutsch. med. Wochenschr.*, 1834 (1913).
Blumenthal, Thallin, Dissert., Dorpat, **1885**.
Bochefontaine, M., Quinoline, *Compt. rend.*, **95**: 1293 (1882).
Bochefontaine, M., Cupreine. *Compt. rend.*, **100**: 366, 644 (1885).
Bodo, R., Quinine, *J. Physiol.*, **64**: 365 (1928).
Boeck, H. von, J. Bauer, Quinine, *Z. Biol.*, **10**: 336 (1874).
Boecker, E., Vuzine, *Deutsch. med. Wochenschr.*, **45**: 1020 (1920).
Boecker, E., Quinine, *Biochem. Z.*, **103**: 63 (1920).
Boenheim, F., Cinchophen, *Z. exptl. Path. Therap.*, **15**: 379 (1914).
Bogen, E., Cinchophen, *Calif. West. Med.*, **35**: 269 (1931).
Bohland, Trypaflavine, *Med. Klin.*, **1919**, 1173; *Deutsch. med. Wochenschr.*, **1919**, 797.
Bokorny, Th., Thalline, *Arch. ges. Physiol.*, **64**: 262 (1892).
Bond, W. R., N. Bloom, Nupercaine, *J. Lab. Clin. Med.*, **16**: 447 (1931).
Bongers, P., Quinine, *Arch. exptl. Path. Pharmakol.*, **35**: 415 (1895).
Borchardt, W., Quinine, *Arch. Schiffs Tropen-Hyg.*, **34**: 360 (1930).
Bovet, M. D., Aminoquinoline, *Arch. intern. pharmacod.*, **41**: 103 (1931).
Boyd, G. H., Quinine, *Am. J. Hyg.*, **6**: 173 (1926).
Boysken, O., Acriflavine, *Muench. Med. Wochenschr.*, **77**: 1362 (1930).
Bradford, J. R., Cytisine, *J. Physiol.*, **8**: 79 (1887).
Brahm, C., Quinosol, *Z. physiol. Chem.*, **28**: 439 (1899).
Bramachari, Upendranath, *et al.*, Quinoline, *J. Pharm. exptl. Therap.*, **41**: 255 (1931); **39**: 413 (1930); **44**: 445 (1932).
Brandesky, W., Nupercaine, *Centr. Chir.*, **58**: 132 (1930).
Braun, A., Yatren, *Muench. Med. Wochenschr.*, **72**: 562 (1925).

Braun, H., H. Schaeffer, Cupreine, *Berlin. klin. Wochenschr.*, **54**: 885 (1917).
Braun, J. von, A. Stuckenschmidt, Cinchophen, *Ber.*, **56**: 1724 (1923).
Braun, J. von, P. Wolff, Cinchophen, *Ber.*, **55**: 3675 (1922).
Braun, L. J., Cinchophen, *J. Med. Assoc. S. Africa*, **3**: 157 (1929).
Breitenstein, A., Yatren, *Centr. Bakt. Parasitenk.*, Abt. I, Orig. **89**: 294 (1922).
Brieger, L., Quinoline, *Z. klin. Med.*, **4**: 296 (1882).
Brody, J. G., Quinidine, *J. Am. Inst. Homeopathy*, **20**: 1102 (1927).
Brosius, O. F., Plasmoquine, *United Fruit Co. Ann. Rept.*, **16**: 26, 52 (1927); **17**: 51 (1928).
Brot, M., Cinchophen, Thèse de Génève, **1923**.
Brouadel, Thalline, Séance acad. Med., Paris, Oct. 22, **1889**.
Brown, O. H., Quinine, *J. Biol. Chem., Proc.* **2**: 70 (1912).
Browning, C. H., J. B. Cohen, Quinoline dyes, *Brit. Med. J.*, **2**: 695 (1921).
Browning, C. H., J. B. Cohen; S. Ellingworth, R. Gulbranson, Acridine, *J. Path. Bact.*, **27**: 121 (1924); Quinoline dyes, *J. Path. Bact.*, **29**: 317 (1926); **31**: 134 (1928); *Proc. Roy. Soc. (London)*, **93**: 329 (1922); **96**: 317 (1924); **100**: 293 (1926); **105**: 99 (1929).
Browning, C. H., J. B. Cohen, R. Gaunt, R. Gulbranson, Acridine, *Proc. Roy. Soc. (London)*, **93**: 329 (1922).
Browning, C. H., N. Gilmour, Acridine, *J. Path. Bact.*, **18**: 144 (1913).
Browning, C. H., R. Gulbranson, Acridine, *J. Pharmacol.*, **34**: 187 (1928); *Brit. J. Exptl. Path.*, **2**: 95 (1921).
Browning, C. H., R. Gulbranson, Kennaway, Acridine, *J. Path. Bact.*, **21**: 106 (1920).
Browning, C. H., R. Gulbranson, Thornton, Acridine, *Brit. Med. J.*, **2**: 70 (1917).
Browning, C. H., J. B. Cohen, K. E. Cooper, R. Gulbranson, Quinoline dyes, *Proc. Roy. Soc. (London)*, **110B**: 372 (1932).
Browning, C. H., J. B. Cohen, J. N. Ashley, R. Gulbranson, Quinoline dyes, *Ibid.*, **110B**: 249 (1932).
Brugsch, Th., H. Horsters, Cinchophen, *Z. ges. exptl. Med.*, **43**: 716 (1924); **38**: 367 (1923).
Brugsch, Th., Wolfenstein, Quinoline, *Berlin. klin. Wochenschr.*, **52**: 157 (1915).
Brunton, T. H., J. T. Cash, Quaternary bases, *Proc. Roy. Soc. (London)*, **35**: 324 (1883).
Buchner, H., F. Fuchs, L. Megele, Alcohol, *Arch. Hyg.*, **40**: 346, 357 (1901).
Buermann, E., Yatren, Inaug. Dissert. Giessen, **1923**.
Bunce, A. H., Plasmoquine, *J. Am. Med. Assoc.*, **45**: 991 (1930).
Burke, V., M. Jess, S. Phillips, Acridine, *J. Infectious Diseases*, **43**: 131 (1928).
Burkhardt, a.Dorn, Acridine, *Brun's Beitr. klin. Chir.*, **119**: 617 (1920).
Burridge, W., Quinine, *Arch. intern. pharmacodynamie*, **34**: 112 (1928).
Bush, A. D., Quinine, *J. Pharmacol.*, **15**: 173 (1920).
Busk, G., Quinoline, *Biochem. Z.*, **1**: 425, 473 (1906).

Cabot, R. C., Cinchophen, *Bost. Med. Surg. J.*, **192**: 1122 (1925).
Cabot, R. C., E. M. Chapman, T. B. Mallory, Cinchophen, *New Engl. J. Med.*, **205**: 153 (1931).
Cahn-Bronner, C. E., Quinine, *Z. exptl. Path. Therap.*, **20**: 307 (1919).
Caujolle, F., Quinine, *Bull. soc. chim. biol.*, **12**: 299 (1930).
Certes, A., Quinoline blue, *Compt. rend.*, **92**: 424 (1881).
Chabrol, E., M. Maximin, Cinchophen, *Presse Médicale*, **37**: 666 (1929).
Chahovitch, X., M. Vichnjicht, Quinine, *J. phys. path. génér.*, **26**: 389 (1928).
Chiba, E., Yatren, *J. Chosen Med. Assoc.*, **19**: (9) (1929).
Chistoni, A., Quinine, *Arch. sci. biol.*, **3**: 53 (1922).
Chopra, R. N., J. C. David, Quinine, *Indian J. Med. Research*, **15**: 343 (1927).

Chopra, R. N., B. B. Dikshit, J. C. David, Cinchonine, *Indian J. Med. Research,* **15**: 571 (1928); **16**: 125 (1928).

Chopra, R. N., B. B. Dikshit, Pillai, Cinchonine, *Indian J. Med. Research,* **17**: 222 (1929).

Chopra, R. N., Choudhurry, Quinine, *Indian J. Med. Research,* **18**: 361 (1929).

Christensen, A., Bromquinine, *J. prakt. Chem.,* new ser., **63**: 313 (1901); **69**: 193 (1904).

Churchill, T. P., F. H. Wagoner, Cinchophen, *Proc. Soc. Exptl. Biol. Med.,* **28**: 581 (1931).

Claus, Loretine, D.R.P. 72,942; *Arch. Pharm.,* **1893**.

Claus and Baumann, Lorentine, *J. prakt. Chem.,* **55**: 457 (1897).

Clerc, A., P. N. Deschamps, Quinine, *Arch. intern. pharmacodynamie,* **28**: 213 (1923).

Clerc, A., C. Pezzi, Quinine, *J. physiol. path. gén.,* **18**: 1174 (1920).

Clerc, A., C. Pezzi, Quinidine, *Paris méd.,* **41**: 440 (1921).

Clerc, A., C. Pezzi, Brochaud, Quinidine, *Compt. rend. soc. biol.,* **89**: 300 (1923).

Coca, A. F., E. F. Grove, Quinine, *J. Immunol.,* **10**: 445 (1925).

Cohen, Kolmer, Heist, Optoquine, *J. Infectious Dis.,* **20**: 272 (1917).

Cohn, J., Cinchonine, *Z. Immunitäts,* **18**: 570 (1913).

Cohn, R., Quinaldine, *Z. physiol. Chem.,* **20**: 210 (1895).

Conitzer, Quinine, *Arch. Gynecol.,* **82**: 349 (1907).

Cooper, S., Quinine, *J. Physiol.,* **59**: xl (1924).

Cordes, W., Plasmoquine, *United Fruit Co. Ann. Rept.,* **16**: 62 (1927); *Arch. Schiffs Tropen-Hyg.,* **32**: 143 (1928).

Cornwall, J. W., Quinine, *Indian J. Med. Research,* **7**: 160 (1919).

Council report, Quinosol, *J. Am. Med. Assoc.,* **54**: 1801 (1910).

Council report, Nupercaine, *Jour. Am. Med. Assoc.,* **96**: 946 (1931).

Crittenden, P. J., Acriflavine, *J. Pharmacol.,* **44**: 423 (1932).

Crohn, Trypaflavine, *Muench. med. Wochenschr.,* **1920**, 1521.

Dadlez, J., W. Kokowski, Phosphine, *Arch. intern. pharmacodynamie,* **38**: 363 (1930).

Dale, H. H., Quinidine, *Heart,* **9**: 87 (1922).

Dale, H. H., P. P. Laidlaw, Cytisine, *J. Pharmacol.,* **3**: 205 (1912-13).

Dale, D., G. R. Mines, Tetrahydroquinaldine, *J. Physiol.,* proc. **42**: xxxi (1911).

Danielsohn, P., Acridine, Inaug. Dissert. Muenchen, **1899**.

Dassen, R., Cinchophen, *Semana méd. (Buenos Aires),* **36**: 368 (1925); *J. Am. Med. Assoc.,* **92**: 1563 (1929).

Dauber, M., Quitenine, *Z. exptl. Path. Therap.,* **21**: 307 (1920).

Davin, E. J., T. S. Schlauch, Hydroxyquinoline, *Am. Med.,* **38**: 9 (1932).

Davis, E. G., Acridine, *Am. J. Med. Sci.,* **161**: 251 (1921).

Davis, E. G., White, Acriflavine, *J. Urol.,* **2**: 299 (1918).

Davis, J. S., Cinchophen, *Am. J. Med. Sci.,* **184**: 555 (1932).

Dawson, W. T., Cinchona alkaloids, *Intern. Clinics,* **2**: ser. 40 (1930).

Dawson, W. T., F. A. Garbade, Quinine, *J. Pharmacol.,* **39**: 417 (1930).

Dawson, W. T., F. A. Garbade, Quinine, *J. Am. Med. Assoc.,* **94**: 704 (1930).

Dawson, W. T., S. P. Newman, Quinine, *J. Am. Med. Assoc.,* **97**: 930 (1931).

De Arric, Quinine, *Proc. Soc. Roy. Bruxelles,* May, **1912**.

De Boer, S., Quinine, *Arch. exp. Path. Pharmakol.,* **94**: 314 (1922).

Deeks, W. E., Plasmoquine, *S. Med. J.,* **23**: 417 (1930).

Demme, R., Quinoline carb. acid., *Therap. Gegenw.,* **2**: 63 (1888).

Dennis, W., Cinchophen, *J. Pharmacol.,* **7**: 601 (1915).

Deutsch, Cinchophen, *Muench. med. Wochenschr.,* (50) (1911).

Dévé, F., Rivanol, *Compt. rend. soc. biol.,* **107**: 682 (1931).

Deyton, C. De W., J. W. Wilson, E. H. Zaus, Nupercaine, *Dental Cosmos,* **74**: 857 (1932); *J. Dental Research,* **12**: 575 (1932).

Diasio, J. S., Hydroxyquinoline, *Military Surgeon,* **70**: 594 (1932).
Dietrich, W., Yatren, *Deutsch. med. Wochenschr.,* **1920**, 1080.
Dietzel, R., K. Soellner, Quinine, *Arch. pharm.,* **268**: 269 (1930).
Dilling, W. J., A. A. Gemmell, Quinine, *J. Obstet. Gynaecol. Brit. Empire,* **36**: 352 (1929).
Disselhorst, R., Quinine, *Arch. path. Anat.,* **113**: 95 (1888).
Dixon, W. E., De Premankur, Quinine, *J. Pharmacol.,* **31**: 407 (1927).
Dodek, S. M., Quinine, *Surg. Gynecol. Obstet.,* **55**: 45 (1932).
Doebner, Giesecke, Cinchophen, *Liebigs Ann.,* **242**: 290 (1887); *Ber.,* **32**: 2276 (1899).
Doebner and Miller, Quinaldine, *Ber.,* **15**: 3075 (1882).
Dohrn, M., Cinchophen, *Muench. med. Wochenschr.,* **59**: 568 (1912); *Z. klin. Med.,* **74**: 444 (1912); *Biochem. Z.,* **43**: 240 (1912); *Therap. Gegenw.,* 196 (1913).
Donath, J., Quinoline, *Ber.,* **14**: 178, 1769 (1881).
Drenowski, A. Kir, Plasmoquine, *Arch. Schiffs Tropen-Hyg.,* **32**: 575 (1928).
Dresel, Quinine, *Krause-Brugsch Handb.,* **10**: 50 (1922).
Drought, Worster C., Cinchophen, *Brit. Med. J.,* **1**: 148 (1923).
Dudgeon, L. S., Quinine, *J. Hyg.,* **18**: 317 (1919).
Durdufi, A., Quinine, *Arch. exp. Path. Pharmakol.,* **25**: 446 (1889).

Eckert, A., Yatren, *Klin. Wochenschr.,* **1922**, 1788.
Eckert, L., Cinchophen, *Pharm. Centralhalle,* **71**: 678 (1930).
Ehrlich, P., Thalline, *Deutsch. med. Wochenschr.,* **12**: 849 (1886).
Ehrlich, P., Quinoline blue, *Therap. Monatsh.,* **1887**, 88.
Ehrlich, P., Thalline, *Therap. Monatsh.,* **1887**, 53.
Ehrlich, P., Flavaniline, *Berlin. klin. Wochenschr.,* **44**: 233, 280, 341 (1907).
Eichhoff, E., Nupercaine, *Centr. Chir.,* (42), 1929.
Eichholtz, F., Plasmoquine, *Arch. Schiffs Tropen-Hyg.,* **31**: Beih. 1, 89 (1927).
Eimer, K., Cinchophen, *Deutsch. med. Wochenschr.,* **57**: 1663 (1931).
Einhorn, A., A. Eichgruen, Methoxydihydroquinoline, *Ber.,* **22**: 1489 (1890).
Eisenberg, Hydrocupreines, *Centr. Bakt. Parasitenk.,* **71**: 422 (1913).
Eisenmeyer, G., H. Quinke, Quinine, *Arch. exptl. Path. Pharmakol.,* **139**: 313 (1929).
Elliot, A. H., Cinchophen, *J. Am. Med. Assoc.,* **97**: 1384 (1931).
Ellison, F. O. B., Cinchonamine, *J. Physiol.,* **43**: 28 (1911).
Ellram, W., Cinchonamine, *Arch. intern. pharmacodynamic,* **9**: 289 (1901).
Elsner, J. R., Tetrophan, *Muench. med. Wochenschr.,* **71**: 699 (1924).
Emde, H., Quinine, *Helv. Chim. Acta,* **15**: 557 (1932).
Emmerich, R., Oxychinaseptol. *Muench. med. Wochenschr.,* **39**: 324 (1892).
Engel, Thalline, *Mitt. Med. Klin. Wuerzburg,* **2**: 135.
Epstein, D., Plasmoquine, *J. Med. Assoc. S. Africa,* **5**: 15 (1931).
Eschbaum, F., Hydrocupreines, *Ber.,* **28**: 397 (1918).
Escher, Villequer, Quinine, *Presse méd.,* **39**: 453 (1931).
Evans, G., Cinchophen, *Brit. Med. J.,* **2**: 93 (1926).
Evers-Agnauer, Quinosol, *Arch. Schiffs Tropen-Hyg.,* **18**: 809 (1914).
Ewald, Kairine, *Berlin klin. Wochenschr.,* **20**: 367 (1883).
Ewins, A. J., Cytisine, *J. Chem. Soc.,* **103**: 97 (1913).

Falk, E., Thalline, *Therap. Monatsh.,* **4**: 211 (1890).
Faludi, F., Cinchophen, *Z. ges. exptl. Med.,* **61**: 127 (1928).
Feiler, M., Quinine, *Arch. Protistenk.,* **61**: 119 (1928).
Feiler, M., Plasmoquine, *Arch. Protistenk.,* **61**: 133 (1928).
Feiler, M., Trypaflavine, *Z. Immunitäts.,* **30**: 95 (1920).
Felton, L. D., K. M. Dougherty, Quinine, *J. Exptl. Med.,* **35**: 761 (1922).
Fenyvessy, B. von, Oxyquinoline, *Z. physiol. Chem.,* **30**: 552 (1900).
Feri, K., Quinine, *Arch. intern. pharmacodynamie,* **21**: 27 (1911).

Filehne, W., Kairine, *Berlin. klin. Wochenschr.,* **19**: 681 (1882); **20**: 77, 283 (1883).

Fine, M. S., A. F. Chace, Cinchophen, *Proc. Soc. Exptl. Biol. Med.,* **11**: 111 (1914).

Fischer, O., Kairine, D.R.P. 21,150, 1884.

Fischer, O., Plasmoquine, *Muench. med. Wochenschr.,* **75**: 1369, 1417 (1928).

Fischer, O., W. Weise, Plasmoquine, *Deutsch. med. Wochenschr.,* **53**: 1380 (1927).

Fleischmann, Trypaflavine, *Klin. Wochenschr.,* **1922**, 217.

Fleming, Trypaflavine, *Lancet,* **1917**, 841.

Foerster, O., Tetrophan, *Klin. Wochenschr.,* **7**: 55 (1925).

Folin, O., H. Lyman, Cinchophen, *J. Pharmacol.,* **4**: 539 (1913).

Fourment, P., H. Hermann, Quinine, *Bull. sci. pharmacol.,* **37**: 348 (1930).

Fourneau, E., Trefouel, Stefanopuolo, Benoit, Lestrange, Melville, Quinine, *Ann. Inst. Pasteur,* **44**: 503, 719 (1930).

Fourneau, E., Trefouel, Bovet, Benoit, Aminoquinoline, *Ann. Inst. Pasteur,* **46**: 514 (1931).

Frank, E., Bauch, Cinchophen, *Berlin. klin. Wochenschr.,* **48**: 1463 (1911).

Frank, E., G. Pietrulla, Cinchophen, *Arch. exptl. Path. Pharmakol.,* **77**: 361 (1914).

Frank, E., Przedborski, Cinchophen, *Arch. exptl. Path. Pharmakol.,* **68**: 349 (1912).

Frank, E., Cinchophen, *Arch. exptl. Path. Pharmakol.,* **151**: 219 (1930).

Franke, Hegler, Eucupine, *Med. Klin.,* **1**: 628 (1920).

Fredericq, H., E. Terroine, Quinine, *J. path. phys. gén.,* **15**: 961 (1913).

Frenzel, W. C., Cinchophen, *Wisconsin Med. J.,* **28**: 264 (1929).

Freund, H., Nupercaine, *Klin. Wochenschr.,* **8**: 1444 (1929).

Freund, H., R. Gottlieb, Yatren, *Arch. exptl. Path. Pharmakol.,* **93**: 92 (1922).

Frey, E., Quinine, *Arch. exptl. Path. Pharmakol.,* **138**: 228 (1928).

Frey, W., Quinidine, *Deutsch. Arch. klin. Med.,* **136**: 70 (1921).

Friedlaender, P., C. F. Gehring, Quinoline, *Ber.,* **16**: 1833 (1883).

Friedlaender, P., Obermaier, Carbostyryl, *Ber.,* **14**: 1916 (1881).

Friedmann, U., Optoquine, *Berlin. klin. Wochenschr.,* **53**: 423 (1916).

Frommherz, K., Cinchophen, *Biochem. Z.,* **35**: 494 (1911).

Fuchs, A., Desoxyquinine, Inaug. Dissert., Muenchen, **1899**.

Fuehner, H., Oxyquinoline, *Ber.,* **38**: 2713 (1906).

Fuehner, H., Quinoline, *Arch. exptl. Path. Pharmakol.,* **55**: 27 (1906).

Fuehner, H., Acridine, *Arch. exptl. Path. Pharmakol.,* **51**: 391 (1904).

Fuehner, H., Nupercaine, *Sammlung. Vergiftungsfällen,* **3B**: 7 (1932); *Arch. exptl. Path. Pharmakol.,* **166**: 462 (1932).

Fuehner, H., E. Mertens, Cytisine, *Biochem. Z.,* **115**: 262 (1921).

Fuerst, K., Cinchophen, *Arch. exptl. Path. Pharmakol.,* **105**: 238 (1925).

Fuerth, O. von, E. Kuh, Neocinchophen, *J. Pharmacol.,* **38**: 57 (1930).

Fuerth, O. von, C. Schwarz, Quinine, *Arch. ges. Phys.,* **129**: 525 (1910).

Fujino, G., Quinine, *Jap. J. Med. Sci.,* **4** *Pharm.,* **5** (1), 61 (1930).

Galeotti, G., Cyanine, *Z. wiss. Mikroscop.,* **11**: 194 (1894).

Gargill, S. L., Cinchophen, *New Engl. J. Med.,* **204**: 183 (1932).

Gay, E. P., L. F. Morrison, Trypaflavine, *J. Infectious Diseases,* **28**: 1 (1921).

Gaza, von, Acridine, *Beitr. klin. Chir.,* **115**: 296 (1919).

Geigy, R., W. Koenigs, Phenylquinaldine, *Ber.,* **18**: 2400 (1885).

Gessner, O., Yatren, *Arch. exptl. Path. Pharmakol.,* **142**: 45, 62 (1929).

Gibbs, O. S., Quinine, *J. Pharmacol.,* **33**: 185 (1928).

Gibbs, O. S., Uric acid, *Science,* **70**: 241 (1929).

Giemsa, G., Yatren, *Z. angew. Chem.,* **41**: 731 (1928).

Giemsa, G., Quinine, *Arch. Schiffs Tropen-Hyg.,* Beih. **30**: 62 (1926); *Muench. med. Wochenschr.,* **74**: 574 (1927).

Giemsa, G., J. Halberkann, Quinine, *Deutsch. med. Wochenschr.,* **43**: 1501 (1917).

Giemsa, G., S. von Prowazek, Quinine, *Arch. Schiffs Tropen-Hyg.*, **12**: Beih. 5, 88 (1908).
Giemsa, G., H. Schaumann, Quinine, *Arch. Schiffs Tropen-Hyg.*, **11**: Beih. 3 (1917).
Giemsa, G., W. Weise, C. Tropp, Quinine, *Arch. Schiffs Tropen-Hyg.*, **30**: 334 (1926).
Giemsa, G., H. Werner, Quinidine, *Arch. Schiffs Tropen-Hyg.*, **18**: 12 (1914).
Girndt, O., Quinidine, *Arch. exptl. Path. Pharmakol.*, **140**: 91 (1929).
Glover, L. R., Cinchophen, *Brit. Med. J.*, **2**: 136 (1926).
Godoy, A., J. G. Lacorte, Plasmoquine, *Compt. rend. soc. biol.*, **98**: 617 (1927).
Gold, H., W. Modell, L. Price, Quinidine, *Arch. Intern. Med.*, **50**: 766 (1932).
Goldhahn, R., Nupercaine, *Klin. Wochenschr.*, **9**: 756 (1930).
Goldmann, Acridine, *Brun's Beitr. klin. Chir.*, **64**: 192 (1909).
Goodson, A. J., T. A. Thomas, J. W. S. Macfie, Quinine, *Biochem. J.*, **24**: 874 (1930).
Gottlieb, R., Quinine, *Arch. exptl. Path. Pharmakol.*, **26**: 419 (1890).
Gough, H. King, p-Aminophenyl arsinic acids, *J. Chem. Soc.*, **132**: 669 (1930).
Grabbe, C., Quinosol, *Arch. exptl. Path. Pharmakol.*, **137**: 96 (1928); **138**: 155 (1928).
Grabe, F., H. Nahme, K. Seelkopf, Hydroxyquinolinium bases, *Arch. exptl. Path. Pharmakol.*, **166**: 172 (1932).
Grabe, F., H. Seelkopf, Quinoline carboxylic acid, *Arch. exptl. Path. Pharmakol.*, **166**: 161 (1932).
Grabfield, J. T., J. H. Pratt, Cinchophen, *J. Pharmacol.*, **42**: 407 (1931).
Graham, A. B., Quinine, *J. Am. Med. Assoc.*, **93**: 1187 (1929).
Green, R., Dimoplasmine, *Lancet*, 1137 (1929).
Green, R., Atrebine, *Lancet*, **222**: 826 (1932).
Greinert, E., Cinchophen, *Arch. exptl. Path. Pharmakol.*, **77**: 458 (1914).
Gremme, A., Nupercaine, *Centr. Gyn.* (25), 1930.
Grethe, G., Quinoline, *Deutsch. Arch. klin. Med.*, **56**: 189 (1895).
Griesbach, W., G. Samson, Cinchophen, *Biochem. Z.*, **94**: 277 (1919).
Grimaux, E., Quinoline, *Compt. rend. acad. France*, 1883, 584.
Grimaux, E., E. Arnaud, Quinine, *Compt. rend.*, **112**: 1364 (1891); **114**: 548, 672.
Grimaux, E., J. V. Laborde, Bourru, Cupreine, *Compt. rend.*, **118**: 1303 (1894).
Grimaux, E., J. V. Laborde, Quinine, *Semaine méd.*, **12**: 432 (1892).
Grimaux, E., J. V. Laborde, Cupreine, *Compt. rend. soc. biol.*, **44**: 608 (1892).
Grolnick, M., Cinchophen, *Med. J. Record*, **132**: 240 (1930).
Grosser, P., Quinine, *Biochem. Z.*, **8**: 98 (1907).
Grossmann, M., Quinine, *Arch. exptl. Path. Pharmakol.*, **97**: 147 (1923).
Grunnenberg, Ullmann, Cinchophen, *Med. Klin.*, **20**: 663 (1924).
Gudzent, F., J. Keip, Lytophan, *Therap. Gegenw.*, **23**: 127 (1921).
Guttmann, P., Kairine, *Berlin. klin. Wochenschr.*, **20**: 465 (1883).

Haas, H., 8-hydroxyquinoline, *Muench. med. Wochenschr.*, **79**: 142 (1932).
Hachija, Yatren, *Tokyo Tjishinshi*, No. 2506, 1927.
Hagen, von, Tetrophan, *Klin. Wochenschr.*, **7**: 943 (1925).
Hahn, M., E. Remy, Trypaflavine, *Deutsch. med. Wochenschr.*, **48**: 793 (1922).
Halberkann, J., Quinine, *Biochem. Z.*, **95**: 24 (1919).
Hale, W., Quinine, *J. Pharmacol.*, **6**: 602 (1915); **8**: 722 (1916).
Halsey, J. T., Chapman, Reynolds, Blackberg, Quinine, *J. Pharmacol.*, **32**: 89 (1927).
Hamburger, H. J., E. Hekma, Quinine, *Biochem. Z.*, **9**: 512 (1908).
Hammet, R., Quinine, *Rev. pharm. thérap.*, **1**: 74 (1927).
Hanzlik, P. J., E. M. Butt, Quinine, *J. Pharmacol.*, **33**: 387 (1928).

Hanzlik, P. J., R. W. Scott, C. M. Weidenthal, J. Fettermann, Cinchophen, *J. Am. Med. Assoc.*, **76**: 1728 (1921).

Hanzlik, P. J., M. Tainter, Cinchophen, *J. Lab. Clin. Med.*, **9**: 166 (1923).

Hardikar, S. W., Quinine, *J. Pharmacol.*, **24**: 395 (1924); **25**: 175 (1925).

Harnack, E., Quinine, *Muench. med. Wochenschr.*, **59**: 1941 (1912).

Harris, K. E., Quinidine, *Heart*, **14**: 283 (1929).

Hartmann, M., E. Wybert, Cinchophen, *Helv. Chim. Acta.*, **2**: 16 (1919).

Hartmann, H., Zilia, Quinine, *Arch. exptl. Path. Pharmakol.*, **83**: 221 (1918).

Hartung, C., Quinosol, *Arch. exptl. Path. Pharmakol.*, **64**: 381 (1911).

Haskell, C. C., Quinidine, *J. Pharmacol.*, **32**: 223 (1928).

Haskins, H. D., Cinchophen, *J. Pharmacol.*, **5**: 63 (1913).

Hasselmann, C. M., M. Hasselmann-Kahlert, Plasmoquine, *Phillip. J. Sci.*, **37**: 75 (1928); *Deutsch. med. Wochenschr.*, **55**: 1635 (1929).

Hata, S., Acridine, *Kitasato Arch. exptl. Med.*, **9**: 1 (1932).

Hatcher, R. A., Cinchophen, *J. Am. Pharm. Assoc.*, **17**: 557 (1928).

Hatcher, R. A., H. Gold, Quinine, *J. Pharmacol.*, **30**: 347 (1927).

Hatcher, R. A., S. Weiss, Quinine, *J. Pharmacol.*, **29**: 279 (1926).

Haudeck, M., Cinchophen, *Wien. klin. Wochenschr.*, **40**: 238 (1927).

Haupt, Trypaflavine, *Centr. Gyn.*, (34), 1921.

Heathcote, R. S. A., A. L. Urquhart, Acriflavine, *J. Pharmacol.*, **38**: 145 (1930).

Hecht, A. F., Rothenberger, Quinidine, *Z. ges. exptl. Med.*, **7**: 134 (1918).

Heffter, A., Quinine, *Muench. med. Wochenschr.*, **1921**, 707; *Arch. exptl. Path. Pharmakol.*, **31**: 254 (1893).

Hegner, R., R. D. Manwell, Plasmoquine, *Am. J. Trop. Med.*, **7**: 279 (1927).

Hegner, R., E. H. Shaw, R. D. Manwell, Quinine, *Am. J. Hyg.*, **8**: 564 (1928).

Heidelberger, M., W. A. Jacobs, Dihydrodesoxyquinine, *J. Am. Chem. Soc.*, **42**: 1489 (1920).

Heidelberger, M., W. A. Jacobs, Dihydroquinicinol, *J. Am. Chem. Soc.*, **44**: 1098 (1920).

Heijningen, Quinidine, *Ann. Chem. Pharmac.*, **72**: 303 (1849).

Heinz, R., Quinoline, *Arch. pathol. Anat.*, **122**: 116 (1890).

Heller, F., Cinchophen, *Berlin. klin. Wochenschr.*, 12 (1913).

Hermann, A., Cinchophen, *Med. Klin.*, **23**: 278 (1927); *Arch. exptl. Path. Pharm.*, **143**: 219 (1931); *Klin. Wochenschr.*, **10**: 1399 (1931).

Herzberg, K., Yatren, *Klin. Wochenschr.*, **9**: 1830 (1922).

Herzig, A. J., Quinine, *N. Y. Med. J.*, **99**: 529 (1914).

Herzig, A. J., Acridine, *Laryngoscope*. **36**: 445 (1926).

Hesse, E., Cinchophen, *Arch. exptl. Path. Pharmakol.*, **158**: 233 (1930).

Hesse, E., Tetrophan, *Arch. exptl. Path. Pharmakol.*, **111**: 68 (1926).

Hesse, Conchinamine, *Liebig's Ann.*, **209**: 62 (1881); *Ber.*, **16**: 59 (1883).

Heubach, H., Quinine, *Arch. exptl. Path. Pharmakol.*, **5**: 1 (1876).

Heubner, W., Quinosol, *Arch. exptl. Path. Pharmakol*, **197**: 91 (1929).

Heubner, W., R. Siegel, Quinosol, *Klin. Wochenschr.*, **5**: 1709 (1926).

Heyl, Guphen, *Pharm. Centralhalle*, **71**: 567 (1930).

Heymans, J. F., Dicarboxylic acid, *Arch. Physiol.*, **1889**, 168.

Hilarowitz, H., J. Bielinski, Nupercaine, *Centr. Chir.*, **58**: 1113 (1931).

Hildebrandt, H., Quinotoxine, *Arch. exptl. Path. Pharmakol.*, **59**: 127 (1908).

Hilgermann, R., Bile, *Muench. med. Wochenschr.*, **77**: 1480 (1930).

Hiramatsu, Y., Quinine, *Jap. J. Med. Sci. Pharmacol.*, **5** (2), 61 (1931).

Hirsch, C., Nupercaine, *Muench. med. Wochenschr.*, **76**: 1715 (1929).

Hirschfelder, A. D., Quinine, *J. Pharmacol.*, **6**: 597 (1915).

Hirschfelder, A. D., H. H. Jensen, W. W. Swanson, Ethoxyquinoline, *Proc. Soc. Exptl. Biol. Med.*, **20**: 402 (1923).

Hirschfelder, A. D., L. J. Pankow, Quinoline, *Proc. Soc. Exptl. Biol. Med.*, **19**: 64 (1922).

Hirschhorn, L., M. G. Mulinos, Quinine, *Proc. Soc. Exptl. Biol. Med.*, **28**: 168 (1930).

Hitzenberger. Cinchophen, *Wein. klin. Wochenschr.*, **40**: 205 (1927).
Hlasiwitz, Quinidine, *Ann. Chem. Pharm.*, **77**: 49 (1851).
Hockett, A. J., Quinine, *Proc. Soc. Exptl. Biol. Med.*, **26**: 613 (1929).
Hoegler, F., Cinchophen, *Wien. klin. Wochenschr.*, **44**: 1246 (1931).
Hoerlein, H., Plasmoquine, *Arch. Schiffs Tropen-Hyg.*, **30**: Beih. 3, 5 (1926).
Hoffmann, A. von, Quinine, *Arch. exptl. Path. Pharmakol.*, *7*: 233 (1877).
Hoffmann, F. B., Quinidine, *Z. Biol.*, **71**: 47 (1920).
Hofmann, A., Quinoline, *Liebig's Ann.*, **47**: 76 (1843).
Hofmann, L., Koenigs, Kairoline, *Ber.*, **16**: 732 (1883).
Hofmann, W., Hydrocupreines, *Centr. Chir.*, **45**: 921 (1918).
Hoppe-Seyler, G., Quinotoxine, *Arch. exptl. Path. Pharmakol.*, **24**: 241 (1888).
Hughes, T. H., D. L. Shrivastava, Quinine, *Indian J. Med. Research*, **14**: 601 (1927).
Humboldt, A. von, Quinine, Versuche über gereizte Muskel und Nervenfasern, **1797**, II, 432 [Binz, *Arch. pathol. Anat.*, **45**: 67 (1869)].
Hunt, Reid, Quinine, *Arch. intern. pharmacodynamie*, **12**: 497 (1904).
Hunt, Reid, R. R. Renshaw, Quaternary Bases, *J. Pharmacol.*, **35**: 99 (1929); **36**: 177 (1929).
Hupfer, Quininic acid, *Z. physiol. Chem.*, **37**: 302 (1903).
Husemann, A., W. Marmé, Cytisine, *Z. Chem.*, **1**: 161 (1865).
Husemann, Th., Quinine, *Therap. Monatsh.*, **2**: 7 (1888).

Igura, S., Quinine, *Folia. endocrin. Jap.*, **3**: 1581 (1928).
Ikeda, Y., Quinine, *J. Pharmacol.*, **8**: 101 (1916).
Impens, E., Cinchophen, *Arch. intern. pharmacodynamie*, **22**: 379 (1912).
Isenschmid, R., Quinine, *Arch. exptl. Path. Pharmakol.*, **75**: 10 (1913).
Israels, M. C., A. D. MacDonald, Nupercaine, *Brit. Med. J.*, **2**: 986 (1931).

Jachia, L., Quinine, *Minerva medica*, **1**: 935 (1930).
Jacksch, R. von, Quinoline, *Z. klin. Med.*, **8**: 442 (1884).
Jackson, C. R., Tetrahydromethylquinoline, *Ber.*, **14**: 889 (1881).
Jackson, D. E., Quinine, *J. Pharmacol.*, **4**: 291 (1913).
Jackson, D. E., A. Friedlaender, J. W. Lawrence, Quinidine, *J. Lab. Clin. Med.*, **7**: 311 (1924).
Jacobs, W. A., M. J. Heidelberger, Quaternary quinine derivatives, *J. Am. Chem. Soc.*, **41**: 2090 (1919).
Jacobs, W. A., M. J. Heidelberger, Aminazole derivatives of quinine, *J. Am. Chem. Soc.*, **42**: 2278 (1920).
Jakobson, Reimer, Quinaldine, *Ber.*, **16**: 1084 (1883).
James, S. P., W. D. Nicol, P. G. Shute, Quinine, *Lancet*, **220**: 1248 (1931); *Trans. Roy. Soc. Trop. Med. Hyg.*, **21**: 233 (1927/28).
Janzen, E., L. K. Wolff, Rivanol, *Nederland Tijdschr. Geneeskunde*, **67**: 1, 2107 (1923).
Jellinek, G., Quinoline, *Monatsh. Chem.*, **7**: 351 (1886).
Jess, A., Quinoline, *Zentr. Biophys. Biochem.*, **18**: 546 (1916).
Jochmann, E., Yatren, *Z. klin. Med.*, **104**: 255 (1926).
Jodlbauer, A., L. Fuerbringer, Phosphine, *Deutsch. Arch. klin. Med.*, **59**: 158 (1897).
Jodlbauer, A., H. Salvendi, Acridine, *Arch. intern. pharmacodynamie*, **15**: 223 (1905).
Johannessohn, F., Quinine, *Berlin. klin. Wochenschr.*, **42**: 1000 (1918).
Johannsen, Cinchonine, Dissert., Dorpat, **1870**.
Jolyet, Cahours, Quaternary Bases, *Compt. rend.*, **66**: 1131 (1868).
Jones, H. W., Nupercaine, *Anesthesia and Analgesia*, **9**: 218 (1930).
Jones, P. H., R. H. Turner, Yatren, *J. Am. Med. Assoc.*, **93**: 583 (1929).
Junkmann, K., Quinine, *Arch. exptl. Path. Pharmakol.*, **105**: 169 (1925).

Kaewel, R., R. Kuehn, Quinine, *Arch. exptl. Path. Pharmakol.*, **125**: 242 (1927).

Kaku, T., Cinchophen, *Acta. Med. Keijo*, **11**: 47 (1928); *Ber. ges. Physiol. exptl. Pharmakol.*, **49**: 136; *Folia. Pharm. Jap.*, **9**: (1), 2 (1929).
Kamei, T., Quinoline, *J. Biochem. Jap.*, **7**: 197 (1927).
Kandidoff, Quinine, *Wien. med. Presse*, (4), **1893**.
Kartagener, M., F. Ramel, Trypaflavine, *Sammlung. Vergiftungsfällen*, **3**: 285 (1932).
Katz, J., Quinine, *Biochem. Z.*, **36**: 144 (1911).
Katzenstein, M., Fr. Schulz, Rivanol, *Klin. Wochenschr.*, **1**: 513 (1922).
Kaufmann, A., Quinine, *Ber.*, **46**: 1823 (1913).
Kaufmann, M., Quinine, *Brun's Beitr. klin. Chir.*, **116**: 666 (1919).
Kauftheil, L., E. Neubauer, Acridine, *Arch. exptl. Path. Pharmakol.*, **116**: 296 (1926).
Kehar, H. D., Cinchona alkaloids, *Indian J. Med. Research*, **18**: 203, 987, 1001 (1931).
Kehrer, Quinine, *Arch. Gyn.*, **81**: 160 (1906).
Kerner, G., Quitenine, *Arch. ges. Physiol.*, **3**: 93 (1870).
Kerner, G., Quinidine, *Z. anal. Chem.*, **1**: 152 (1862).
Keyes, E. L., A. M. McLellan, Nupercaine, *J. Am. Med. Assoc.*, **96**: 2085 (1931).
Keysser, Fr., Vuzine, *Brun's Beitr. klin. Chir.*, **96**: 1 (1919).
Keysser, Fr., Trypaflavine, *Med. Klin.*, **1921**, 411; *Z. Chir.*, **162**: 94 (1921).
Kikuchi, I., Quinine, Tohoku, *J. Exptl. Med.*, **11**: 116 (1928).
Kikuth, W., Atebrine, *Deutsch. med. Wochenschr.*, **58**: 530 (1932); *Riv. malariol.*, **11**: (2) (1932).
Kindt, B., H. Vollmer, Naphthoquinoline, *Arch. exptl. Path. Pharmakol.*, **148**: 198 (1930).
Kingren, O., Cinchophen, *Deutsch. med. Wochenschr.*, **40**: 238 (1927).
Kirchner, W., Quinine, *Berlin. klin. Wochenschr.*, **18**: 725 (1881).
Kirschbaum, W., Quinine, *Klin. Wochenschr.*, **2**: 1404 (1923).
Klapp, R., Acridine, *Deutsch. med. Wochenschr.*, **47**: 1383 (1921).
Kleine, Quinine, *Z. Hyg. Infektionskrankh.*, **38**: 458 (1901).
Klemperer, C., Cinchophen, *Therap. Gegenw.*, **15**: 257 (1913).
Klestadt, W., Nupercaine, *Muench. med. Wochenschr.*, **76**: 2009 (1929).
Kliegler, J. J., R. Reitler, Pasmoquine, *Riv. malariol.*, **8**: 28 (1929).
Klinkert, Cinchophen, *Klin. Wochenschr.*, **6**: 24 (1927); *Therap. Gegenw.*, **69**: 149 (1928).
Klose, F., Vuzine, *Deutsch. med. Wochenschr.*, **45**: 901 (1919).
Klotz, M., Quinine, *Therap. Halbmonatsh.*, **34**: 141 (1920).
Kneuppel, Quinoline, *Ber.*, **29**: 703 (1896).
Kobert, R., Kairine, *Arch. exptl. Path. Pharmakol.*, **22**: 92 (1887).
Kobert, R., Cytisine, *Deutsch. med. Wochenschr.*, **16**: 406 (1890).
Koenigs, W., Lepidine, *Ber.*, **23**: 2673 (1890).
Koenigs, W., Quinoline, *Ber.*, **12**: 453 (1879).
Koenigs, W., Quinotoxine, *Ber.*, **40**: 648 (1907).
Koenigs, W., Desoxyquinine, *Ber.*, **28**: 3143 (1895); **29**: 372 (1896).
Koenigs, W., Jaeglé, Quinaldine, *Ber.*, **28**: 1046 (1895).
Koenigs, W., Meimberg, Tetrahydroquinoline, *Ber.*, **28**: 1042 (1895).
Koenigs, W., Mengel, Lepidine, *Ber.*, **37**: 1328 (1904).
Koenigs, W., J. H. Nef, Quinaldinic acid, *Ber.*, **19**: 2427 (1886).
Kofler, L., W. Dernbach, Cinchophen, *Arch. Pharm.*, **170**: 153 (1932).
Kosakae, J., Quinine, *Kiuki Fjuikw. Gak. Z.*, **11**: 38 (1928).
Kraepelin, E., Cytisine, *Neurol. Centr.* (1) **1888**.
Krebs, H. A., Quinosol, *Biochem. Z.*, **220**: 289, 296, 300 (1930).
Krehl, L. von, Matthes, Kairine, *Arch. exptl. Path. Pharmakol.*, **38**: 284 (1897).
Kronacher, Oxychinaseptol, *Muench. med. Wochenschr.*, **39**: 328 (1892).
Kroo, H., F. O. Schultz, Quinine, *Deutsch. med. Wochenschr.*, **53**: 1759 (1927).
Krumwiede, C., H. E. Mann, Quinine, *J. Infectious Diseases*, **16**: 24 (1915).
Kuehnel, W., Nupercaine, *Ugeskrift for laeger*, **93**: 924 (1931); *J. Am. Med. Assoc.*, **97**: 1842 (1931).

Kuester, E., H. Wolff, Quinoline, *Berlin. klin. Wochenschr.*, **56**: 123 (1919).
Kumagawa, M., Thalline, *Arch. path. Anat.*, **113**: 134 (1888).
Kunkel, A. J., Quinine, *Toxicology*, **2** Ed., 1744 (1901).
Kuno, J., Quinine, *Folia Pharmacol. Japon.*, **9**: (4), 21 (1930).
Kura, G., Quinine, *Folia Pharmacol. Japon.*, **13**: (3), 21 (1932).
Kurdinowski, E. M., Quinine, *Arch. Gyn.*, **78**: 34 (1906).
Kusnetzow, A. J., Cytisine, *Arch. exptl. Path. Pharmakol.*, **135**: 333 (1928).
Kusui, K., Quinoline, *Jap. J. Biochem.*, **13**: 343 (1931).

La Franca, S., Cinchophen, *Biochem. Z.*, **35**: 434 (1911).
Landerer, Quinine, 1836 [Merkel, *Arch. exptl. Path. Pharmakol.*, **47**: 165 (1902)].
Lane, C., Quinine, *Trop. Diseases Bull.*, **21**: 849 (1924).
Langdon, Brown, Cinchophen. *Brit. Med. J.*, **2**: 37 (1926).
Lange, R., Quinine. *Therap. Monatsh.*, **33**: 384 (1919).
Langecker, H., Quinine. *Arch. exptl. Path. Pharmakol.*, **118**: 49 (1926).
Langer, H., Acridine, *Deutsch. med. Wochenschr.*, **46**: 1015 (1920); *Z. ges. exptl. Med.*, **27**: 174 (1922); **28**: 45 (1922).
Langlois, Cinchonine, *Arch. phys. path. gén.*, **25**: 377 (1893).
Laqueur, E., Optoquine, *Ergebnisse intern. Med. Kinderheilk.*, **23**: 467 (1924).
Laqueur, E., Quinine, *Arch. exptl. Path. Pharmakol.*, **55**: 240 (1906).
Laqueur, E., R. Magnus, Acridine, *Z. ges. exptl. Med.*, **13**: 31 (1921).
Laqueur, E., A. Sluyters, L. K. Wolff, Rivanol, *Z. ges. exptl. Med.*, **42**: 247 (1924).
Larreglo, S., Quinine, *Siglio Med. Madrid*, **85**: 661 (1930).
Laubender, W., W. Ost, Nupercaine, *Arch. exptl. Path. Pharmakol.*, **165**: 520 (1932).
Laveran, A., "Traité des fièvres palustres," **1884**.
Le Heux, J. W., C. de Lind van Wyngaarden, Plasmoquine, *Arch. exptl. Path. Pharmakol.*, **144**: 341 (1929); *Klin Wochenschr.*, **4**: 857 (1927); *Arch. neerland. physiol.*, **14**: 324 (1930).
Leineweber, Quinine, Inaug. Dissert., Goettingen, **1883**.
Lenox, W. G., Uric acid, *J. Biol. Chem.*, **66**: 521 (1925).
Lenz, E., Arcidine, *Z. ges. exptl. Med.*, **12**: 195 (1921).
Levrat, M., A. Badinand, Acriflavine, *J. méd. Lyon,* **1931**, 21.
Lewin, L., Quinine, *Arch. exptl. Path. Pharmakol.*, **60**: 324 (1909).
Lewis, P. M., Cinchophen, *J. Florida Med. Assoc.*, **16**: 219 (1929).
Lewis, Th., Quinidine, *Am. J. Med. Sci.*, **143**: 781 (1922).
Lewis, Th., A. W. Drury, Quinidine, *Heart*, **13**: 95 (1926).
Lewis, Th., A. W. Drury, Iliescu, Wedd, Quinidine, *Brit. Med. J.*, **2**: 514 (1921).
Lichtman, S. S., Cinchophen, *Arch. Intern. Med.*, **48**: 98 (1931).
Liebig, J. von, Quinine, *Liebig's Ann.*, **153**: 152 (1870).
Liese, W., Quinosol, *Centr. Bact.*, **105**: Orig., 137 (1927).
Lim, C. E., Kurotchkin, P. J., Rivanol, *Natl. Med. J. China*, **16**: 215 (1930).
Lipschitz, W., Hydrocupreines, *Centr. Bact.*, **90**: 569 (1923).
Lipschitz, W., Freund, Hydrocupreines, *Arch. exptl. Path. Pharmakol.*, **99**: 226 (1923).
Lipschitz, W., W. Laubender, Nupercaine, *Klin. Wochenschr.*, **8**: 1438 (1929); **9**: 756, 968 (1930).
Loening, K., Cinchophen, *Therap. Monatsh.*, **28**: 123 (1913).
London letter, Cinchophen, *J. Am. Med. Assoc.*, **90**: 1229 (1928).
Loew, A., R. Pfeiffer, Quinine, *Wien. klin. Wochenschr.*, **40**: 526 (1927).
Loew, A., A. Krema, Quinine, *Wien. klin. Wochenschr.*, **41**: 1453 (1928).
Loewe, S., Quinolylethylamine, *Z. ges. exptl. Med.*, **6**: 335 (1918).
Loewenstein, E., Quinine, *Z. Hyg.*, **84**: 317 (1917).
Loewenstein, E., S. Neuschloss, Quinine, *Z. Hyg.*, **84**: 257 (1917).
Loewenstein, E., S. Neuschloss, W. Kosian, Quinine, *Z. Hyg.*, **84**: 325 (1917).
Loewenthal, L. J., W. A. Macay, E. C. Loewe, Cinchophen, *Brit. Med. J.*, **1**: 592 (1928).

Love, W. S., Quinidine, *Heart,* **13**: 87 (1926).
Lublin, A., Cinchophen, *Arch. exptl. Path. Pharmakol.,* **155**: 331 (1930).
Lusk, G. W. C., Quinosol, *Proc. Soc. Exptl. Biol. Med.,* **16**: 104 (1919).
Luzatto, R., R. Ciusa, Cinchophen, *Arch. farm. sper.,* **16**: 6 (1913).

Maas, Analgen, *Z. Klin. Med.,* **28**: 139 (1895).
MacCarrison, R., J. W. Cornwall, Quinine, *Indian J. Med. Research,* **6**: 248 (1919).
MacDonald, A. D., M. G. Israels, Nupercaine, *J. Pharmacol.,* **45**: 359 (1932).
MacDonald, E., Quinine, *J. Am. Med. Assoc.,* **64**: 505 (1915).
MacGilchrist, A. C., Quinine, *J. Am. Med. Assoc.,* **65**: 1588 (1915).
MacKendrick, J. G., Quinoline, *Brit. Med. J.,* **1**: 954, (94) (1878).
MacKendrick, J. G., J. Dewar, Quinoline, *Ber.,* **7**: 1458 (1874) ; *Proc. Roy. Soc. (London)*, **23**: 290 (1875) ; **22**: 432 (1874).
MacLean, A. D., Quinine, *J. Am. Med. Assoc.,* **68**: 1290 (1917).
MacLeaster, Cinchophen, *Arch. Intern. Med.,* **12**: 739 (1913).
MacPhail, N. P., Plasmoquine, *United Fruit Co. Ann. Rept.,* **16**: 67 (1927).
MacVicar, J. F. Weir, Cinchophen, *Med. Clin. N. Am.,* **12**: 1526 (1929).
Macht, D. J., Quinine, *J. Pharmacol.,* **34**: 137 (1928).
Macht, D. J., E. J. Teagarden, Quinine, *J. Pharmacol.,* **22**: 21 (1923).
Mann, L., Tetrophan, *Klin. Wochenschr.,* **1**: 2573 (1922).
Mannaberg, J., Phosphine, *Deutsch. Arch. klin. Med.,* **59**: 185 (1897).
Mannifold, J. A., Plasmoquine, *J. Roy. Army Med. Corps,* **56**: 321, 410 (1931).
Manson-Bahr, P., Plasmoquine, *Brit. Med. J.,* **1**: 466 (1927).
Manson-Bahr, P., Quinine, *Lancet,* **220**: 843 (1931).
Manwaring, W. H., H. O. Ruh, Quinine, *J. Exptl. Med.,* **9**: 473 (1907).
Marcacci, Quinine, *Arch. ital. biol.,* **9**: 2 (1888).
Marmé, W., Cytisine, *Therap. Monatsh.,* **1**: 156 (1887).
Martino, G., G. Carbonaro, Quinine, *Boll. soc. ital. biol. sper.,* **3**: 218 (1928).
Martinotti, G., Cyanine, *Z. wiss. Microscop.,* **5**: 305 (1888).
Marx, H., Quinine, *Arch. exptl. Path. Pharmakol.,* **54**: 460 (1906).
Matao, Y., Cinchophen, *Folia Pharmacol. Japon.,* **12**: (1), 4 (1931).
Matsuda, S., Apoquinine, *Jap. J. Med. Sci. Pharm.,* **5**: (3) 40 (1931).
Maurel, M. E., Quinine, *Compt. rend. soc. biol.,* **55**: 367 (1903).
Maurer, Quinine, *Deutsch. med. Wochenschr.,* **33**: 173 (1907).
Maxcy, K. F., Quinine, *U. S. Pub. Health Rept.,* **37**: 693 (1922) ; *J. Am. Med. Assoc.,* **91**: 1372 (1928) : proceedings of the celebration of 300th anniversary of the first recognized use of cinchona, St. Louis, 1930, 241.
Meier, R., Yatren, *Arch. exptl. Path. Pharmakol.,* **122**: 129 (1927).
Meldolesi, G., Cinchonine, *Cuore Circulat.,* **9**: 353 (1925).
Meleney, F. L., Z. Zau, Acriflavine, *J. Am. Med. Assoc.,* **84**: 337 (1925).
Memmi, G., Schulemann, Plasmoquine, *Riv. malariol.,* **6**: 40 (1927) ; *Klin. Wochenschr.,* **6**: 1093 (1927).
Mendel, B., Cinchophen, *Deutsch. med. Wochenschr.,* **25**: 829 (1922).
Menk, W., Plasmoquine, *United Fruit Co. Ann. Rept.,* **16**: 78 (1927).
Mering, J. von, Kairine, *Z. klin. Med., Suppl.* **7**: 149 (1884).
Merkel, A., Quinine, *Arch. exptl. Path. Pharmakol.,* **47**: 165 (1902).
Merkel, G., Kairine, *Deutsch. Arch. klin. Med.,* **34**: 100 (1884).
Methner, Th., Quinaldine, *Ber.,* **27**: 2689 (1894).
Meyer, E., H. Reinhold, Quinine, *Klin. Wochenschr.,* **5**: 1619 (1926).
Meyer, J. L., Acriflavine, *Am. J. Obstet. Gynecol.,* **20**: 760 (1930).
Michael, H., Yatren, *Klin. Wochenschr.,* **1**: 1153 (1922).
Michaelis, L., K. J. Dernby, Quinine, *Z. Immunitäts.,* **34**: 194 (1922).
Michaelis, L., Hayashi, Trypaflavine, *Z. Immunitäts.,* **36**: 518 (1923).
Milanesi, E., Quinine, *Arch. farm. sper.,* **46**: 29 (1928).
Miller, H. Th., Cinchophen, *J. Am. Med. Assoc.,* **96**: 772 (1931).
Miller, J. J., Jr., O. R. McCoy, W. L. Bradford, Acriflavine, *J. Am. Med. Assoc.,* **98**: 1242 (1932).
Miller, W. von, Quinoline, *Ber.,* **23**: 2252 (1890).

Millzner, R. J., C. D. Leake, Eurupine, *Proc. Soc. Exptl. Biol. Med.*, **26**: 526 (1929).
Miura, K., Apoquinine, *Jap. J. Med. Sci. Pharm.*, **5**: (1), 1 (1930).
Miura, K., Y. Sogen, Apoquinine, *Jap. J. Med. Sci. Pharm.*, **5**: (3) 41 (1931).
Moellendorf, von, Acridine, *Ergebnisse Physiol.*, **18**: 141 (1920).
Moldovan, J., Quinine, *Z. Biochem.*, **47**: 421 (1912).
Monasterio, G., Trypaflavine, *Arch. exptl. Path. Pharmakol.*, **159**: 172 (1931).
Monasterio, G., Acriflavine, *Minerva Med.*, **1**: 540 (1931).
Moncorvo, Analgen, *Therap. Monatsh.*, **11**: 501 (1897).
Montmollin, E. De, Quinine, *Thèse de Génève*, **1919**.
Moon, V. H., Quinine, *Jour. Infectious Diseases*, **13**: 165 (1913); **16**: (1) (1915).
Moore, Ethylhydrocupreine, *J. Exptl. Med.*, **22**: 269 (1915).
Morgenroth, J., Quinine. *Berlin. klin. Wochenschr.*, **54**: 55 (1917).
Morgenroth, J., Optoquine. *Berlin. klin. Wochenschr.*, **51**: 1829, 1865 (1914).
Morgenroth, J., Hydrocupreines. *Deutsch. Med. Wochenschr.*, **44**: 961 (1918).
Morgenroth, J., L. Abraham, Cupreines, *Deutsch. med. Wochenschr.*, **16**: 57 (1920).
Morgenroth, J., R. Bieling, Hydrocupreine, *Berlin. klin. Wochenschr.*, **54**: 723 (1917).
Morgenroth, J., E. Bumke, Hydrocupreines, *Deutsch. med. Wochenschr.*, **44**: 729 (1918).
Morgenroth, J., E. Bumke, Optoquine, *Deutsch. med. Wochenschr.*, **40**: 539 (1914).
Morgenroth, J., S. Ginsberg, Hydrocupreines, *Berlin. klin. Wochenschr.*, **50**: 343 (1913).
Morgenroth, J., J. Halberstaedter, Quinine, *Sitzsber. kgl. preuss. Akad. Wiss.*, **1910**, 732; **1911**, 30; *Berlin. klin. Wochenschr.*, **48**: 1558 (1911).
Morgenroth, J., Levy, Optoquine, *Berlin. klin. Wochenschr.*, **48**: 1560, 1979 (1911).
Morgenroth, J., R. Schnitzer, E. Rosenberg, Rivanol, *Deutsch. med. Wochenschr.*, **47**: 1317 (1921).
Morgenroth, J., Tugendreich, Hydrocupreines, *Berlin. klin. Wochenschr.*, **53**: 794 (1916).
Morgenroth, J., Tugendreich, Optoquine, *Biochem. Z.*, **79**: 257 (1917).
Morris, W., Cinchophen, *Brit. Med. J.*, **1**: 221 (1931).
Motzfeld, K., Cinchophen, *Norsk. Mag. Laegevidenskap.*, **90**: 283 (1929); *J. Am. Med. Assoc.*, **92**: 1724 (1929).
Muehlens, P., Plasmoquine, *Arch. Schiffs Tropen-Hyg.*, **30**: Beih. 3; **31**: Beih. 1, 7 (1927); *Deutsch. med. Wochenschr.*, **53**: 1933 (1927).
Muehlens, P., Atrebine, *Muench. med. Wochenschr.*, **79**: 537 (1932).
Muehlens, P., W. Kirschbaum, Plasmoquine, *Arch. Schiffs Tropen-Hyg.*, **28**: 131 (1924).
Mueller, A. von, Cinchophen, *Therap. Monatsh.*, **28**: 468 (1913).
Mueller, Fr., Kairine, *Mitt. Wuerzburg. med. Klin.*, **2**: 136.
Murakami, K., Quinine, *Okayama-Igakkai-Zasshi*, **42**: (7) (1930); *Jap. J. Med. Sci. Pharm.*, **5**: (1), 62 (1930).
Myers, C. V., J. A. Killian, Cinchophen, *J. Pharmacol.*, **18**: 213 (1921).
Myers, H. B., L. Goodman, Cinchophen, *Arch. intern. Med.*, **49**: 946 (1932).

Nahme, H., Benzolsulphonic acid, *Arch. exptl. Path. Pharmakol.*, **166**: 157 (1932).
Nahme, H., K. Seelkopf, Yatren, *Arch. exptl. Path. Pharmakol.*, **166**: 126 (1932).
Nakano, N., Quinine, *Folia pharmacol. Japon.*, **3**: (2), 7 (1927).
Napier, L. E., B. M. Das Gupta, Atebrine, *Indian Med. Gaz.*, **47**: 181 (1932).
Napier, L. E., D. Butcher, B. M. Das Gupta, Atebrine, *Indian Med. Gaz.*, **47**: 186 (1932).

Nasse, O., Quinine, *Arch. ges. Physiol.*, **11**: 138 (1875).

Nelson, E. E., Quinine, *J. Pharmacol.*, **31**: 209 (1927); *Arch. intern. pharmacodynamie,* **33**: 186, 204 (1927); *Proc. Soc. Exptl. Biol. Med.*, **25**: 499 (1928).

Nelson, E. E., F. W. Thomas, Quinine, *Arch. intern. pharmacodynamie,* **31**: 455 (1927).

Nencki, Krolikowski, Kairine, *Sitzsber. Akad. Wiss. Wien., Math. naturw. Kl. I, IIa, IIb, III,* **9**: 208 (1888).

Neuberg, C., Hydrotropism, *Biochem. Z.*, **76**: 107 (1916).

Neufeld, F., O. Schiemann, Trypaflavine, *Deutsch. med. Wochenschr.*, **45**: 844 (1919).

Neufeld, F., O. Schiemann, Optoquine, *Centr. Bact.*, Ref. **57**: 57, Beih. 163 (1913).

Neufeld, F., O. Schiemann, Baumgarten, Acridine, *Deutsch. med. Wochenschr.*, **46**: 1013 (1920).

Neumann, Eucupine, *Berlin klin. Wochenschr.*, **55**: 191 (1918).

Newman, W. W., Quinidine, *J. Am. Med. Assoc.*, **91**: 1268 (1928).

Niccolaier, A., M. Dohrn, Cinchophen, *Deutsch. Arch. klin. Med.*, **93**: 331 (1908).

Niccolini, P. M., Quinine, *Boll. ital. soc. biol. sper.*, **3**: 698 (1928).

Nicoletti, V., Trypaflavine, *Giorn. ital. dermat. e sif.*, **73**: 366 (1932).

Niederehe, W., Quinoline, *Z. ges. exptl. Med.*, **6**: 350 (1918).

Nierenstein, N., Quinine, *J. Roy. Army Med. Corps.*, **32**: 215, 218 (1919).

Nierenstein, E., Acridine, *Arch. ges. Physiol.*, **179**: 233 (1920).

Nishi, M., Quinine, *Arch. exptl. Path. Pharmakol.*, **60**: 312 (1909).

Nocht, B., W. Kikuth, Quinine, *Arch. Schiffs Tropen-Hyg.*, **33**: 355 (1929).

Oechsner, Hydroquinoline, *J. prakt. Chem.*, **1882**, 1079.

Oettingen, W. F. von, E. E. Ecker, Yatren, *Proc. Soc. Exptl. Biol. Med.*, **28**: 1029 (1931).

Ogden, K., R. Adams, Cinchoninic acid, *J. Am. Chem. Soc.*, **47**: 826 (1925).

Ohlson, E., Quinine, *Arch. intern. pharmacodynamie.* **37**: 108 (1930).

Okamoto, H., Apoquinine, *Jap. J. Med. Sci. Pharm.*, **5**: (1), 2 (1930).

Okamoto, H., Quinine. *Proc. Jap. Pharm. Soc.*, **4**: 40 (1930).

Okamoto, H., K. Miura, Quinine, *Kanazawa Ikw. Daig. Juzenkw. Zasshi,* **33**: 674 (1928).

Okamoto, H., Y. Sogen, Apoquinine, *Jap. J. Med. Sci. Pharm.*, **5**: (1), 4 (1930).

Okonogi, T., Quinine, *Jap. J. Med. Sci. Pharm.*, **4**: 73 (1930).

O'Mally, Richer, Quinine, *Arch. Intern. Med.*, **24**: 378 (1910).

Orachowitz, D., Plasmoquine. *Arch. Schiffs Tropen-Hyg.*, **32**: 119 (1928).

Orator, V., Walchshofer. Cinchophen. *Deutsch. Z. Chir.*, **205**: 86 (1927).

Orenstein, A. J., Atebrine, *Brit. Med. J.*, **2**: 8 (1932).

Oschatz, F., Quinoline, Inaug. Dissert. Goettingen, **1882**.

Oshika, H., Santoninic acid, *Acta. School Med. Univ. Imp. Kioto*, **4**: 281, 421 (1921).

Ostermeyer, Diquinolinedimethyl sulfate, *Ber.*, **17**: 2444 (1884).

Palm, A., Diiodo-8-hydroxyquinoline, *Arch. exptl. Path. Pharmakol.*, **166**: 176 (1932).

Paolini, R., Quinine, *Arch. patol. clin. Med.*, **7**: 409 (1928).

Parkinson, J., M. Campbel, Quinidine. *Quat. J. Med.*, **22**: 281 (1929).

Parson, L., W. S. Harding, Cinchophen. *Am. J. Med. Sci.*, **181**: 115 (1931).

Peter, F. M., Yatren, *Dermatol. Wochenschr.*, **84**: 615 (1927).

Peter, F. M., Atebrine, *Deutsch. med. Wochenschr.*, **58**: 533 (1932).

Pezzi, C., A. Clerc, Quinine, *Presse Med.*, **28**: 334 (1920).

Pfitzinger, W., Cinchophen, *J. prakt. Chem.*, **33**: 100 (1886); **38**: 582 (1888); **56**: 283 (1892); **66**: 263 (1902).

Phelbs, B. M., Plasmoquine, *United Fruit Co. Ann. Rept.*, **16**: 70 (1927).

Phillips, J., Cinchophen, *J. Am. Med. Assoc.*, **61**: 1040 (1913).

Piccinini, G. M., Quinine, *Arch. intern. pharmacodynamie*, **32**: 225 (1926).

Pillsbury, C. D., Plasmoquine, *J. Am. Med. Assoc.*, **95**: 991 (1930).

Piung-Hun Ri, Cinchophen, *Jap. J. Med. Sci., Pharm.*, **5**: (3) 27 (1931).
Plugge, P. C., Tetrahydroquinoline, *Arch. intern. pharmacodynamie*, **3**: 173 (1897).
Pohl, J., Hydroatophan, *Z. exptl. Path. Therap.*, **19**: 198 (1918).
Porak, R., Quinine, *J. Trop. Med. Hyg.*, **21**: 138 (1918).
Prevot, Binet, Cytisine, *Rev. med. Suisse Rom.*, **7**: 516, 533 (1887); **8**: 670 (1888).
Pringle, Quinine, "Observations on the diseases of the army," Ed. V, London, p. 20, **1765**.
Prinz, A., Yatren, *Muench. med. Wochenschr.*, **68**: 1215 (1921).
Prior, Quinine, *Arch. ges. Physiol.*, **34**: 237 (1884).
Prowazek, S. von, Quinine, *Arch. Protistenk.*, **18**: 221 (1910).

Raab, O., Acridine, *Z. Biol.*, **39**: 524 (1900).
Rabe, P., Quinotoxine, *Ber.*, **38**: 2770 (1905); **40**: 2013, 3280 (1907).
Rabe, P., Cinchinone, *Ber.*, **41**: 62 (1908).
Rabe, P., K. Kindler, Quinotoxine, *Ber.*, **51**: 1360 (1918).
Rabe, P., W. Huntenberg, A. Schultze, G. Volger, Hydroquinine, *Ber.*, **44**: 2487 (1931).
Rabinowitz, M. A., Cinchophen, *J. Am. Med. Assoc.*, **95**: 1228 (1930).
Rabinowitz, M. A., Cinchophen, *Med. Clin. N. Am.*, **11**: 1025 (1928).
Rabuteau, M., Quaternary bases, *Compt. rend.*, **76**: 887 (1873).
Radziwillowicz, R., Cytisine, *Arb. pharm. Inst. Dorpat*, **2**: 56 (1888).
Rake, G. W., Cinchophen, *Guy's Hosp. Rept.*, **77**: 229 (1927).
Reaves, R. G., Acriflavine, *Arch. otolaryng.*, **7**: 166 (1928).
Redenze, C. de, Cinchophen, *Brasil. Med.*, **41**: 1005 (1927).
Rehns, J., Hydroquinoline, *Arch. intern. pharmacodynamie*, **8**: 199 (1901).
Reichle, H. S., Cinchophen, *Arch. Intern. Med.*, **44**: 281 (1929); **49**: 215 (1932).
Reinhardt, Trypaflavine, *Z. Infektionskrankh.*, **95**: 27 (1922).
Renescu, N., D. Dorogan, Quinine, *Arch. exptl. Path. Pharmakol.*, **167**: 251 (1932).
Retzlaff, K., Cinchophen, *Z. exptl. Path. Therap.*, **12**: 307 (1913).
Retzlaff, K., Quinine, *Z. exptl. Path. Therap.*, **22**: 65 (1921).
Rhode, H., Quinine, *Arch. exptl. Path. Pharmakol.*, **91**: 173 (1921).
Richet, C., R. Conder, Acriflavine, *Bull. mém. soc. méd. hop.* Paris, **54**: 1690 (1930).
Richter, P., Quinine, *Arch. path. Anat.*, **123**: 118 (1891).
Riddle, O., C. E. Anderson, Quinine, *Am. J. Physiol.*, **47**: 92 (1918).
Riess, L., Kairine, *Berlin. klin. Wochenschr.*, **20**: 817 (1883).
Riesser, O., Quinine, *Z. physiol. Chem.*, **130**: 176 (1923).
Rikl, A., Irritans, *Arch. exptl. Path. Pharmakol.*, **133**: 192 (1928).
Risi, A., Cinchophen, *Arch. intern. pharmacodynamie*, **42**: 117 (1932).
Ritter, A., Trypaflavine, *Deutsch. Z. Chir.*, **159**: 13 (1920).
Rivière, R., *et al.*, Acriflavine, *Compt. rend. soc. biol.*, **106**: 346 (1931).
Robertson, T. Braisford, Quinine, *J. Biol. Chem.*, **1**: 515 (1905).
Robin, Thalline, *Séances acad. méd. Paris*, Oct. 15th, **1889**.
Roehl, W., Plasmoquine, *Arch. f. Schiffs Tropen-Hyg.*, **30**: Beih. 3, 11 (1926).
Roesler, Jarczyk, Cinchophen, *Deutsch. Arch. klin. Med.*, **107**: 573 (1912).
Roethlisberger, P., Cinchophen, *Rev. méd. suisse Rom.*, **40**: 172 (1920).
Rohde, E., Quinine, *Heffter's Handb. exptl. Pharmakol.*, **2**: (1), 76 (1920).
Rohde, G., A. Antonaz, Quinine, *Ber.*, **40**: 2329 (1907).
Rona, P., E. Bloch, Quinine, *Biochem. Z.*, **118**: 185 (1920).
Rona, P., H. W. Nicolai, Quinine, *Biochem. Z.*, **189**: 331 (1927).
Rona, P., D. Reinicke, Quinine, *Biochem. Z.*, **108**: 213 (1920).
Ronnefeldt, F., Plasmoquine, *Muench. med. Wochenschr.*, **78**: 420 (1931).
Rosenbaum, S., Eucupine, *Deutsch. med. Wochenschr.*, **1**: 521 (1920).
Rosenberg, H., Uric acid, *Z. exptl. Path. Therap.*, **14**: 245 (1913).
Rosenhain, F., Cynurenic acid, Inaug. Dissert, Koenigsberg, **1886**.
Rosenstein, P., Rivanol, *Deutsch. med. Wochenschr.*, **47**: 1320 (1921).
Rosenstein, S., Nupercaine, *Deutsch. med. Wochenschr.*, **55**: 2010 (1929).

Rosenstein, W., Quinine, *Compt. rend.*, **130**: 752 (1900).
Rosenthal, J., Quinoline, *Deutsch. Arch. klin. Med.*, **42**: 206 (1888).
Rosenthal, E., W. Lipschitz, Quinine, *Arch. exptl. Path. Pharmakol.*, **116**: 39 (1926).
Roskin, Gr., K. Romanowa, Quinine, *Z. Immunitäts.*, **62**: 147 (1929).
Ross, J. B., Cinchophen, *Can. Med. Assoc. J.*, **24**: 632 (1931).
Rost, E., Quinosol, *Arb. kaiserl. Gesundh.*, **15**: 288 (1899).
Roth, G. B., Quinine, *J. Pharmacol.*, **3**: 470 (1911); **4**: 157 (1913).
Rotter, L., Cinchophen, *Z. exptl. Path. Therap.*, **19**: 176 (1918).
Rudnick, D. F., Hydroxyquinoline, *Ill. Med. J.*, **62**: 144 (1932).
Runge, M., Quinine, *Centrl. Gyn.*, **4**: 49 (1880).
Rusicka, L., C. F. Seidel, Fr. Liebel, Quinotoxine, *Helv. Chim. Acta.*, **7**: 995 (1924).

Sabatani, A., Quinine, *Arch. farm. sper.*, **50**: 72 (1929).
Sadler, E. S., Dilling, Gemmell, Quinine, *J. Obstet. Gynaecol. Brit. Empire*, **37**: 529 (1930).
Sahashi, Y., 2,6-Quinolinediol, *Bull. Inst. Phys. Chem. Res.*, **9**: 362 (1930).
Samaja, M., Quinine, *J. Am. Med. Assoc.*, **70**: 1267 (1918).
Samura, S., Quinine, *Folia Pharmacol. Japon.*, **11**: (2), 12 (1930).
Sanders, J. P., Quinine, *J. Am. Med. Assoc.*, **97**: 850 (1931).
Sanders, J. P., W. T. Dawson, Quinidine, *J. Am. Med. Assoc.*, **99**: 1773 (1932).
Sanjo, K., Quinine, *Folia Pharmacol. Japon.*, **13**: (3), 28 (1932).
Santesson, C. G., Quinine, *Arch. exptl. Path. Pharmakol.*, **30**: 411 (1892); **32**: 321 (1893); **84**: 176 (1919).
Santesson, C. G., Quinoline, *Arch. exptl. Path. Therap.*, **35**: 23 (1895).
Santesson, C. G., Quinine, *Z. exptl. Path. Therap.*, **24**: 159 (1921).
Santesson, C. G., G. Koraen, Quinine, *Scand. Arch. Physiol.*, **10**: 201 (1900).
Saul, E., Alcohols, *Arch. klin. Chir.*, **56**: 686 (1898).
Schaeffer, H., Hydrocupreines, *Berlin. klin. Wochenschr.*, **53**: 1041 (1916); *Biochem. Z.*, **83**: 269 (1917).
Schaffler, E., Cinchophen, *Z. ges. exptl. Med.*, **57**: 672 (1927).
Schallworth, W. W., Plasmoquine, *Muench. med. Wochenschr.*, **76**: 274 (1929).
Schaumann, O., Rivanol, *Arch. Schiffs Tropen-Hyg.*, **32**: Beih. 4, 16 (1928).
Scheinfinkel, L., Hydrocupreines, *Z. Biol.*, **88**: 407 (1929).
Schelling, Cinchophen, *Muench. med. Wochenschr.*, **73**: 362 (1927).
Schepelmann, E., Quinine, *Therap. Gegenw.*, **13**: 545 (1911).
Schereschewsky, J., Quinine, *Deutsch. med. Wochenschr.*, **56**: 921 (1930).
Scheunemann, B., Quinoline, *Arch. exptl. Path. Pharmakol.*, **100**: 51 (1923).
Schikorr, R., Cinchophen, *Arch. exptl. Path. Pharmakol.*, **168**: 190 (1932).
Schilling, C., Schulze, Quinine, *Deutsch. med. Wochenschr.*, **56**: 46 (1930).
Schilling, W., E. Boeker, Quinine, *Deutsch. med. Wochenschr.*, **45**: 683 (1919).
Schittenhelm, R. Ullmann, Cinchophen, *Z. exptl. Path. Therap.*, **12**: 360 (1913).
Schleimer, H., Cinchophen, *Wien. med. Wochenschr.*, **82**: 610 (1932).
Schlesinger, R., Nupercaine, *Arch. exptl. Path. Pharmakol.*, **160**: 479 (1931).
Schlossberger, H., Acridine, *Centr. Bact. Orig.*, **110**: 210 (1929).
Schmidt, A., Quinoline, Inaug. Dissert., Koenigsberg, **1884**.
Schmiedeberg, Schulten, Cynuren, *Liebig's Ann.*, **164**: 155 (1872).
Schmitt, Engelmann, Quinoline carboxylic acid, *Ber.*, **20**: 1217 (1887).
Schmitz, R., Quinine, *Arch. exptl. Path. Pharmakol.*, **56**: 301 (1907).
Schnabel, A., Optoquine, *Biochem. Z.*, **112**: 112 (1920).
Schnabel, A., Quinine, *Biochem. Z.*, **122**: 285 (1921).
Schnitzer, R., E. Rosenberg, Rivanol, *Klin. Wochenschr.*, **1922**, 2383; *Deutsch. med. Wochenschr.*, **50**: 133 (1924).
Schroeder, H., Cinchophen, *J. Pharmacol.*, **46**: 461 (1932).

Schroeder, H., B. B. Raginsky, Cinchophen, *Arch. exptl. Path. Pharmakol.*, **168**: 413 (1932).
Schroeder, K., Quinine, *Arch. exptl. Path. Pharmakol.*, **72**: 361 (1913).
Schroeder, K., Cinchophen, *Ugsk. Laeger.*, **84**: 1141 (1922); *J. Am. Med. Assoc.*, **79**: 2046 (1922).
Schuebel, K., Yatren, *Klin. Wochenschr.*, 318 (1924).
Schuebel, K., Quinine, *Muench. med. Wochenschr.*, **78**: 1681 (1931).
Schuhmacher, L., Quinine, *Arb. Pharm. Inst. Dorp.*, **10**: 1 (1894).
Schulemann, W., Acridine, *Biochem. Z.*, **80**: 1 (1912); *Z. exptl. Path. Therap.*, **11**: 307 (1912).
Schulemann, W., G. Memmi, Plasmoquine, *Klin. Wochenschr.*, **6**: 1093 (1927).
Schulemann, W., F. Schoenhoefer, A. Wingler, Plasmoquine, *Klin. Wochenschr.*, **11**: 381 (1932).
Schwartz, G., Cinchophen, *Wien. klin. Wochenschr.*, **40**: 238 (1927).
Schwartze, E. W., G. A. Billinghurst, Chiniofon, *J. Pharmacol.*, **45**: 273 (1932).
Secher, K., Quinine, *Arch. exptl. Path. Pharmakol.*, **78**: 445 (1915).
Sée, G., Bochefontaine, Cinchonine, *Compt. rend.*, **100**: 366 (1885).
Seelkopf, K., F. Bender, H. Nahme, E. Schulze, Hydroxyquinoline, *Arch. exptl. Path. Pharmakol.*, **166**: 166 (1932).
Seelkopf, K., H. Nahme, Quinoline sulphonic acid, *Arch. exptl. Path. Pharmakol.*, **166**: 150 (1932).
Seggelke, K., Quinine, *Therap. Halbmonatsh.*, **35**: 17 (1921).
Seibel, J. M., Cinchophen, *Am. Med.*, **38**: 119 (1932).
Semura, S., Quinine, *Folia Pharmacol. Japon.*, **11**: 12 (1930).
Senta, S., Quinine, *Arch. intern. pharmacodynamie*, **18**: 217 (1908).
Sergent, E. a. E., A. Catanei, F. Trensz, A. Sergent, Plasmoquine, *Ann. Inst. Pasteur*, **47**: 57 (1931).
Sergent, E., A. Catanei, Quinine, *Ann. Inst. Pasteur Alger.*, **4**: 35 (1926).
Seto, F., Quinine, *Folia Pharmacol. Japon.*, **6**: 205 (1927).
Severin, Tetrahydroatophan, *Berlin. klin. Wochenschr.*, 830 (1918).
Shahan, W. E., Quinine, *Am. J. Ophth.*, **33**: 136 (1916).
Shaw, E. R., Jr., Quinine, *Am. J. Hyg.*, **8**: 583 (1928).
Sheehan, W. J., Flavine, *Brit. Med. J.*, **1**: 822 (1930).
Sheehan, H. L., Aminoquinoline, *J. Path. Bact.*, **35**: 589 (1932).
Sherwood, K. K. a. H. H., Cinchophen, *Arch. Intern. Med.*, **48**: 82 (1931).
Shizuaki, T., Quinoline, *Acta Schol. Med. Univ. Imp. Kioto*, **6**: 449 (1924).
Siebner, M., Nupercaine, *Chirurg.*, **1**: 1113 (1929).
Singer, G., Quinine, *Wien. klin. Wochenschr.*, **40**: 1261 (1927).
Singer, S., Cinchophen, *Wien. klin. Wochenschr.*, **40**: 238 (1927).
Sinton, J. A., Quinine, *Indian J. Med. Research*, **18**: 831 (1931).
Sinton, J. A., W. Bird, Plasmoquine, *Indian J. Med. Research*, **16**: 159 (1928).
Sinton, J. A., S. Smith, D. Pottinger, Plasmoquine, *Indian J. Med. Research*, **17**: 793 (1930).
Sioli, F., Plasmoquine, *Arch. Schiffs Tropen-Hyg.*, **30**: Beih. 3, 18 (1926).
Sioli, F., Atebrine, *Deutsch. Med. Wochenschr.*, **58**: 531 (1932).
Skita, Brunner, Tetrahydrocinchophen, *Ber.*, **49**: 1601 (1916).
Skorczewski, W., J. Sohn, Cinchophen, *Wien. klin. Wochenschr.*, **25**: 593 (1912); *Z. exptl. Path. Therap.*, **11**: 255 (1912).
Skraup, Z. H., p-Oxytetrahydroquinoline, *Monatsh. Chem.*, **6**: 767 (1883).
Skraup, Z. H., p-Oxyquinoline, *Monatsh. Chem.*, **3**: 545 (1883).
Skraup, Z. H., Quinoline, *Monatsh. Chem.*, **2**: 139 (1882); *Wien. Akad. Ber.*, **81**: (2) 593 (1880).
Smith, M. J., B. Fantus, Optoquine, *J. Pharmacol.*, **8**: 53 (1916).
Smorodinzew, J. A., Quinine, *Biochem. Z.*, **195**: 1 (1928); *Rusk. Z. trop. Med.*, **6**: 73 (1928).
Sollmann, T., Quinotoxine, *J. Am. Med. Assoc.*, **76**: 999 (1921).
Sonak, M., Plasmoquine, *Deutsch. Arch. klin. Med.*, **166**: 168 (1930).
Sonn, A., F. Bernischke, Alkyloxyquinoline, *Ber.*, **54**: 1730 (1921).

Sonntag, Yatren, *Muench. Med. Wochenschr.*, **68**: 573 (1921).
Spaeth, E., Cytisine, *Monatsh. Chem.*, **40**: 15, 93 (1919).
Specht, O., Vuzine, *Brun's Beitr. klin. Chir.*, **1920**, 288.
Speyer, Th. von, Quinine, *Klin. Monatsh. Augenheilk.*, **53**: 393 (1914).
Spiess, G., Trypaflavine, *Deutsch. med. Wochenschr.*, **46**: 511 (1920).
Spurling, R. G., E. E. Hartman, Neocinchophen, *J. Pharmacol.*, **30**: 185 1927) ; *J. Lab. Clin. Med.*, **13**: 854 (1928).
Stacy, L. J., F. R. Vazant, Cinchophen, *Minn. Med.*, **13**: 327 (1930).
Stadelmann, E., Quininic acid, *Arch. exptl. Path. Pharmakol.*, **10**: 317 (1879).
Stadler, H., Alcohol, *Arch. Hyg.*, **73**: 195 (1911).
Stake, T., Quinine, *Scand. Arch. Physiol.*, **57**: 52, 77 (1929).
Starkenstein, E., Quinine, *Muench. med. Wochenschr.*, **66**: 205 (1919).
Starkenstein, E., Cinchophen, *Arch. exptl. Path. Pharmakol.*, **65**: 177 (1911) ; *Biochem. Z.*, **106**: 139, 172 (1920) ; *Z. ges. exptl. Med.*, **43**: 449 (1924).
Starkenstein, E., Salus, Wiechowski, Cinchophen, *Prag. med. Wochenschr.*, **3**: 136 (1913).
Starkenstein, E., Wiechowski, Cinchophen, *Centrl. Biochem. Biophys.*, **17**: 565 (1914).
Steel, M., A. Goerner, F. L. Haley, Quinine, *J. Lab. Clin. Med.*, **17**: 139 (1931).
Stein, S., Hydroxyquinoline, *Laryngoscope*, **42**: 219 (1932).
Steinmetzer, K., Cinchophen, *Wien. klin. Wochenschr.*, **39**: 49-50 (1926).
Stelwagon, H. W., Quinine, *Trans. Am. Derm. Assoc.*, 25th ann. meet., 164, 1901.
Stephan, Trypaflavine, *Med. Klin.*, (17), **1921**.
Stern, R., Cinchophen, *Biochem. Z.*, **159**: 192 (1925).
Stockman, R., Quinoline, *J. Phys.*, **15**: 245 (1894).
Stohr, R., Nupercaine, *Sammlung. Vergiftungsfällen*, **2**: 43 (1931).
Stoute, D. G., Quinine, *Lancet*, **223**: 565 (1932).
Stransky, E., Cinchophen, *Z. ges. exptl. Med.*, **66**: 73 (1929).
Strassburg, J., Quinine, *Arch. exptl. Path. Pharmakol.*, **2**: 334 (1874).
Strickland, C., D. N. Roy, Atebrine, *Indian Med. Gas.*, **67**: 191 (1932).
Struempel, A., Conchinine, *Berlin. klin. Wochenschr.*, **15**: 679 (1878).
Stuehlinger, Kairine, *Arch. exptl. Path. Pharmakol.*, **43**: 166 (1899).
Sugata, H., A. L. Tatum, Quinine, *J. Pharmacol.*, **21**: 293 (1923).
Susuki, H., Quinine, *Keijo J. Med.*, **2**: (2) 1, 12, 23 (1931) ; *Folia. Pharmacol. Japon.*, **11**: (3), 20 (1931).
Sutton, D. L., Cinchophen, *J. Am. Med. Assoc.*, **91**: 310 (1928).

Tagami, M., Acridine, *Tohoku J. exptl. Med.*, **18**: 482 (1932).
Takats, G. de, Eucupine, *Surg., Gynecol. Obstet.*, **43**: 100 (1926).
Takatsuki, S., Nupercaine, *Okayama-Igakkai-Zasshi*, **44**: 587 (1932).
Tannhauser, Cinchophen, *Deutsch. med. Wochenschr.*, **7**: 174 (1927).
Tappeiner, H. von, Phosphine, *Deutsch. Arch. klin. Med.*, **56**: 369 (1895).
Tappeiner, H. von, A. Jodlbauer, Acridine, *Deutsch. Arch. klin. Med.*, **80**: 427 (1904).
Tatum, A. L., R. A. Cutting, Quinine, *J. Pharmacol.*, **20**: 393 (1922).
Taubmann, G., Cinchophen, *Arch. exptl. Path. Pharmakol.*, **121**: 204 (1927).
Tavel, Tomarkin, Vioform, *Deutsch. Z. Chir.*, **55**: 557 (1900).
Taylor, J. A., Quinine, *Brit. Med. J.*, 113 (1920).
Taylor, K., Quinine, *Brit. Med. J.*, **2**: 923 (1915) ; *Lancet*, **1915**, 538.
Teichmann, F., Quinine, *Deutsch. med. Wochenschr.*, **43**: 1092 (1917).
Ten Doerschate, Storm vanLeeuwen, Optoquine, *Nederland Tijdschr. Geneesk.*, **2**: 676 (1917).
Thomson, Kairine, Inaug. Dissert., Dorpat., **1886**.
Thomson, E., Nupercaine, *Ugeskr. Laeger*, **93**: 922 (1931).
Thonnard-Neumann, E., Plasmoquine, *United Fruit Co. Ann. Rept.*, **18**: 56 (1920).
Thunberg, T., Quinoline, *Scand. Arch. Physiol.*, **29**: 1 (1913).

Timm, F., Nupercaine, *Sammlung Vergiftungsfällen*, **3**: 215 (1932).
Tinker, M. B., H. B. Simon, Acridine, *J. Am. Med. Assoc.*, **88**: 1560 (1927).
Traube, J., Quinine, *Biochem. Z.*, **42**: 470 (1912).
Traube, J., Hydrocupreine, *Z. Immunitäts.*, **29**: 286 (1920).
Traube, J., Hegler, Eucupine, *Med. Klin.*, **1**: 628 (1920).
Trendelenburg, P., Quinine, *Arch. exptl. Path. Pharmakol.*, **69**: 79 (1912).
Treuherz, W., Acriflavine, *Dermat. Wochenschr.*, **90**: 317 (1930).
Troendle, A., Quinine, *Biochem. Z.*, **112**: 259 (1920).
Tschernorutzky, H., Quinine, *Biochem. Z.*, **46**: 112 (1912).
Tskimanauri, G., Plasmoquine, *Arch. Schiffs Tropen-Hyg.*, **35**: 89 (1931).
Tubby, Ferguson, Mackie, Hirst, Trypaflavine, *Lancet*, **1919**, 251, 838.

Uhlmann, Fr., Nupercaine, *Arch. intern. pharmacodynamie*, **36**: 253 (1929); *Narcose Anaesthesie*, (6), 1929.
Uhlmann, Fr., R. Burow, Atoquinol, *Schweiz. med. Wochenschr.*, **2**: 416 (1921).
Ullmann, H., Cinchophen, *Z. ges. exptl. Med.*, **32**: 319 (1923).
Ulrici, H., Uric acid, *Arch. exptl. Path. Pharmakol.*, **46**: 321 (1901).

Vajda, E., Cinchophen, *Med. Klin.*, **26**: 1404 (1930).
Valenti, A., Quinine, *Arch. farm.*, **18**: 246 (1914).
Van der Horst, C. H., Quinine, *J. Am. Med. Assoc.*, **71**: 2032 (1918).
Van Winkle, R., W. G. Christiansen, Quinosol, *J. Am. Pharm. Assoc.*, **18**: 794 (1929).
Veley, V. H., A. B. Waller, Quinidine, *J. Physiol.*, **39**: proc. xix (1909).
Virchow, Quinine, *Arch. exptl. Path. Pharmakol.*, **127**: 28 (1927).

Wachtel, M., Nupercaine, *Centr. Gynecol.*, **53**: 2799 (1929).
Waddell, J. A., Quinine, *J. Pharmacol.*, **9**: 279 (1917).
Waddell, J. A., M. Cohn, Quinidine, *J. Lab. Clin. Med.*, **9**: 821 (1924).
Wahl, C. C., P. K. Knoefel, Nupercaine, *Proc. Soc. Exptl. Biol. Med.*, **29**: 368 (1932).
Walker, W. G., Cinchophen, *New Engl. J. Med.*, **204**: 253 (1931).
Waser, E., "Synth. org. Arzeneimittel," Ferd. Enke, Stuttgart, **1928**.
Waters, E. E., Quinoidine, *Indian Med. Gaz. Calcutta*, **51**: 335 (1916).
Weber, S., Quinine, *Arch. exptl. Path. Pharmakol.*, **58**: 93 (1908).
Weichardt, W., Hydroxyquinoline, *Klin. Wochenschr.*, **8**: 1669 (1929).
Weicker, B., Hydroxyquinoline, *Arch. exptl. Path. Pharmakol.*, **166**: 123 (1932).
Weil, P., Cinchophen, *Med. Welt*, **2**: 257 (1928).
Weintraud, W., Novatophan, *Therap. Gegenw.*, **13**: 97 (1911).
Weis, C. R., Cinchophen, *J. Am. Med. Assoc.*, **99**: 21 (1932).
Weise, W., Quinine, *Abhandl. Ges. Auslandsk.*, **D26**: ii, 5 (1928).
Weiss, S., R. A. Hatcher, Quinidine, *J. Pharmacol.*, **30**: 335 (1927); **30**: 327 (1927).
Weiss, Quininic acid, *Z. physiol. Chem.*, **25**: 393 (1898); **27**: 216 (1898).
Wells, C. J. L., Cinchophen, *Brit. Med. J.*, **2**: 759 (1926).
Wels, Acridine, *Z. ges. exptl. Med.*, **28**: 347 (1922).
Wenkebach, Quinidine, *Berlin. klin. Wochenschr.*, **55**: 521 (1918).
Werbitzki, F. W., Acridine, *Centr. Bact. Protistenk.*, **53**: 303 (1910).
Werner, Insipine, *Arch. Schiffs Tropen-Hyg.*, **16**: Beih. 1, 37 (1912).
Whitaker, E. J., Plasmoquine, *United Fruit Co. Ann. Rept.*, **18**: 54 (1929); **16**: 76 (1927).
Whitmore, E. R., Plasmoquine, *United Fruit Co. Ann. Rept.*, **18**: 30 (1929).
Whitmore, E. R., C. M. Roberts, W. Jantzen, Plasmoquine, *United Fruit Co. Ann. Rept.*, **18**: 37 (1929).
Wiechmann, E., Quinidine, *Z. exptl. Med.*, **7**: 155 (1918).
Wiedenhorn, H., Nupercaine, *Arch. klin. Chir.*, **159**: (4) (1930).
Wilcox, W. H., Cinchophen, *Brit. Med. Jour.*, **2**: 273 (1926).
Wilkinson, Quinine, *Brit. Med. J.*, **2**: 836 (1896).
Williams, J., Lepidine, *Jahresber. Fortschr. Chem.*, **1885**, 550.

Williams, J., Methylquinolinium, *Jahresber. Fortschr. Chem.*, **1886**, 534.
Willimott, St. G., Quinine, *Lancet,* **221**: 1133 (1931).
Willisch, Trypaflavine, *Klin. Therap. Wochenschr.* (31-32), 1920.
Winfield, G. A., Cinchophen, *Can. Med. Assoc. J.,* **26**: 170 (1932).
Winogradow, A. P., Cinchophen, *Arch. exptl. Path. Pharmakol.,* **126**: 17 (1927).
Wirgin, G., Alcohol, *Z. Hyg.,* **46**: 149 (1904).
Wirth, S., Nupercaine, *Ugeskr. Laeger,* **93**: 925 (1931).
Wittmaak, K., Quinine, *Arch. ges. Physiol.,* **95**: 203 (1903).
Wollny, W. O., Tetrophan, *Muench. Med. Wochenschr.,* **71**: 833 (1924).
Worster Drought, C. C., Cinchophen, *Brit. Med. J.,* **1**: 148 (1923).
Wright, A. E., Optoquine, *Lancet,* **1912**, 1632, 1701.
Wurtz, Quinoline, *Compt. rend.,* **95**: 263 (1882).
Wyschnegradsky, Tetrahydroquinoline, *Ber.,* **13**: 1481 (1879).

Yamagami, M., Cinchophen, *Folia. Pharmacol. Japon,* **12**: 3 (1931).
Yeo, J. Burney, Quinine, *Trans. Clin. Soc. London,* **22**: 193 (1889) ; *Lancet,* **1889**, 533.
Yorke, M., J. W. S. Macfie, Quinine, *Lancet,* **1924**, 1017.

Zanda, G. B., Quinine, *Arch. intern. pharmacodynamic,* **20**: 415 (1910).
Ziegner, H., Nupercaine, *Centr. Chir.,* **56**: 2770 (1929).
Zieler, Birnbaum, Yatren, *Muench. med. Wochenschr.,* **1922**, 664.
Zimmer, A., Yatren, "Orale Reiztherapie," Leipzig, F. C. W. Vogel, **1926**.
Zipf, K., Quinine, *Arch. exptl. Path. Pharmakol.,* **140**: 56 (1929).
Zulzer, G., Cinchophen, *Berlin. klin. Wochenschr.,* **48**: 2101 (1911).

SUBJECT INDEX

AUTHOR INDEX

American Chemical Society

MONOGRAPH SERIES

PUBLISHED

No.

1. **The Chemistry of Enzyme Actions (Revised Edition).** By K. George Falk.
2. **The Chemical Effects of Alpha Particles and Electrons (Revised Edition).** By Samuel C. Lind.
3. **Organic Compounds of Mercury.** By Frank C. Whitmore.
4. **Industrial Hydrogen.** By Hugh S. Taylor.
5. **Zirconium and Its Compounds.** By Francis P. Venable.
6. **The Vitamins (Revised Edition).** By H. C. Sherman and S. L. Smith.
7. **The Properties of Electrically Conducting Systems.** By Charles A. Kraus.
8. **The Origin of Spectra.** By Paul D. Foote and F. L. Mohler.
9. **Carotinoids and Related Pigments.** By Leroy S. Palmer.
10. **The Analysis of Rubber.** By John B. Tuttle.
11. **Glue and Gelatin.** By Jerome Alexander.
12. **The Chemistry of Leather Manufacture (Revised Edition).** By John A. Wilson. Vol. I. and Vol. II.
13. **Wood Distillation.** By L. F. Hawley.
14. **Valence and the Structure of Atoms and Molecules.** By Gilbert N. Lewis.
15. **Organic Arsenical Compounds.** By George W. Raiziss and Jos. L. Gavron.
16. **Colloid Chemistry (Revised Edition).** By The Svedberg.
17. **Solubility.** By Joel H. Hildebrand.
18. **Coal Carbonization.** By Horace C. Porter.
19. **The Structure of Crystals (Revised Edition).** By Ralph W. G. Wyckoff.
20. **The Recovery of Gasoline from Natural Gas.** By George A. Burrell.
21. **The Chemical Aspects of Immunity (Revised Edition).** By H. Gideon Wells.
22. **Molybdenum, Cerium and Related Alloy Steels.** By H. W. Gillett and E. L. Mack.
23. **The Animal as a Converter of Matter and Energy.** By H. P. Armsby and C. Robert Moulton.
24. **Organic Derivatives of Antimony.** By Walter G. Christiansen.
25. **Shale Oil.** By Ralph H. McKee.
26. **The Chemistry of Wheat Flour.** By C. H. Bailey.
27. **Surface Equilibria of Biological and Organic Colloids.** By P. Lecomte du Noüy.
28. **The Chemistry of Wood.** By L. F. Hawley and Louis E. Wise.
29. **Photosynthesis.** By H. A. Spoehr.
30. **Casein and Its Industrial Applications.** By Edwin Sutermeister.

[*Continued*]

AMERICAN CHEMICAL SOCIETY MONOGRAPH SERIES

PUBLISHED

No.

31. **Equilibria in Saturated Salt Solutions.** By Walter C. Blasdale.
32. **Statistical Mechanics as Applied to Physics and Chemistry.** By Richard C. Tolman.
33. **Titanium.** By William M. Thornton, Jr.
34. **Phosphoric Acid, Phosphates and Phosphatic Fertilizers.** By W. H. Waggaman.
35. **Noxious Gases.** By Yandell Henderson and H. W. Haggard.
36. **Hydrochloric Acid and Sodium Sulfate.** By N. A. Laury.
37. **The Properties of Silica.** By Robert B. Sosman.
38. **The Chemistry of Water and Sewage Treatment.** By Arthur M. Buswell.
39. **The Mechanism of Homogeneous Organic Reactions.** By Francis O. Rice.
40. **Protective Metallic Coatings.** By Henry S. Rawdon.
41. **Fundamentals of Dairy Science.** By Associates of Rogers.
42. **The Modern Calorimeter.** By Walter P. White.
43. **Photochemical Processes.** By George B. Kistiakowsky.
44. **Glycerol and the Glycols.** By James W. Lawrie.
45. **Molecular Rearrangements.** By C. W. Porter.
46. **Soluble Silicates in Industry.** By James G. Vail.
47. **Thyroxine.** By E. C. Kendall.
48. **The Biochemistry of the Amino Acids.** By H. H. Mitchell and T. S. Hamilton.
49. **The Industrial Development of Searles Lake Brines.** By John E. Teeple.
50. **The Pyrolysis of Carbon Compounds.** By Charles D. Hurd.
51. **Tin.** By Charles L. Mantell.
52. **Diatomaceous Earth.** By Robert Calvert.
53. **Bearing Metals and Bearings.** By William M. Corse.
54. **Development of Physiological Chemistry in the United States.** By Russell H. Chittenden.
55. **Dielectric Constants and Molecular Structure.** By Charles P. Smyth.
56. **Nucleic Acids.** By P. A. Levene.
57. **The Kinetics of Homogeneous Gas Reactions.** By Louis S. Kassel.
58. **Vegetable Fats and Oils.** By George S. Jamieson.
59. **Fixed Nitrogen.** By Harry A. Curtis.
60. **The Free Energies of Some Organic Compounds.** By G. S. Parks and H. M. Huffman.
61. **The Catalytic Oxidation of Organic Compounds in the Vapor Phase.** By L. F. Marek and Dorothy A. Hahn.
62. **The Effect of Radiant Energy on Physiological Processes.** By H. Laurens.
63. **The Chemical Refining of Petroleum.** By V. Kalichevsky and B. A. Stagner.

IN PREPARATION

Electrokinetic Phenomena and Their Application to Biology and Medicine. By H. A. Abramson.

Piezo-Chemistry. By L. H. Adams.

The Biochemistry of the Fats and Related Substances. By W. R. Bloor.

Absorptive Carbon. By N. K. Chaney.

The Manufacture of Sulfuric Acid. By Andrew M. Fairlie.

Liquid Ammonia as a Solvent. By E. C. Franklin.

Arsenical and Argentiferous Copper. By J. L. Gregg, G. L. Craig and F. Sillers, Jr.

Surface Energy and Colloidal Systems. By W. D. Harkins and T. F. Young.

The Structure of Rubber. By Ernst A. Hauser.

Manufacture of Soda with Special Reference to the Ammonia Process. By Te Pang Hou.

Raw Materials of Lacquer Manufacture. By J. S. Long.

The Corrosion of Alloys. By Robert J. McKay.

Significance of Manganese, Iron and Aluminum to Soil Acidity and Plant Life. By Forman T. McLean.

Physical and Chemical Properties of Glass. By Geo. W. Morey.

Metabolic Action of Insulin. By John R. Murlin.

Acetylene. By J. A. Nieuwland.

Furfural. By F. N. Peters, Jr., and H. J. Brownlee.

Carbon Dioxide. By Elton L. Quinn and Charles L. Jones.

Aliphatic Sulfur Compounds. By E. Emmet Reid.

The Chemistry of Intermediary Metabolism. By Wm. C. Rose.

Electrical Precipitation of Suspended Particles from Gases. By W. A. Schmidt and Evald Anderson.

Mineral Metabolism. By A. T. Shohl.

Precise Electric Thermometry. By W. P. White and E. F. Mueller.

Modern Theories of Electrolytes. By John Warren Williams.

Ergosterol. By A. Windaus.

Measurement of Particle Size and Its Application. By L. T. Work.